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RENAL PAPILLARY NECROSIS

Roentgenologic diagnosis and formation of calculi

by

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A necrotic lesion of the renal papillae known as papillitis necroticans, necrotizing renal papillitis or renal papillary necrosis sometimes occurs in infection of the urinary tract (15, 23, 31). Three clinically distinct forms may be recognized: an acute fulminating process, in which death ensues in a few days or weeks, a subacute course extending over several months (26), and a chronic condition that may last several years, with remissions and exacerbations (6, 7).

The disease was formerly regarded as rare and the outcome as generally fatal (15), but in recent years treatment with antibiotics and resection or nephrectomy has often enabled the course of the disease to be changed, with the result that the number of chronic cases reported has risen (1, 14). There have been occasional instances where treatment has been said to result in complete recovery (10, 30).

In acute cases, a diagnosis of renal papillary necrosis is usually not made until autopsy but in others the diagnosis can be made ante-mortem through passed papilla fragments or radiologic examination (12, 26, 36). It has hitherto been considered difficult to make a diagnosis solely from a radiologic examination (6, 14).

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It is our purpose to show that the sub-acute and chronic forms of papillary necrosis are not uncommon and that with the aid of improved roentgen technique an ante-mortem diagnosis can be made in the vast majority of cases. Moreover, it will be shown that in chronic cases there is a marked tendency towards the formation of calculi in which detached necrotic papillae often compose the nucleus. This has been demonstrated by microradiography of specimens obtained either on micturition or by surgical removal, a method that may be used in early stages for verifying the diagnosis before definite roentgenologic evidence is available.

Survey of the literature

Since 1877, when the condition was first described by VON FRIEDREICH (12) a total of 194 cases of renal papillary necrosis had, according to ANTHONISEN (2) been published by 1953 (including 3 of his own). Of these, 118 had diabetes mellitus, and 52 obstruction in the urinary tract, while 24 presented neither of these conditions. FRIEDREICH and others held that the disease originates in an obstruction of the urinary tract, possibly without simultaneous infection (12). In 1937 FROBOESE (13) and GÜNTHER (16) pointed out the close association of the disease with diabetes mellitus, while admitting that this condition was not always present. Other authors have declared that the coincident occurrence of the two diseases is due entirely to the diabetic's general susceptibility to infection (30). To-day, most workers regard pyelonephritis as the basic cause (10, 15) and do not attribute papillary necrosis to any particular type of bacteria (31). The extension of the necrosis in the kidney has proved to be independent of the severity of the inflammatory changes of the urinary tract (16). In patients who also have diabetes the ratio of females to males is 2 : 1, and where there is urinary tract obstruction the ratio is 1 : 6 (30).

The necrotic changes are invariably limited to the medullary substance and do not encroach on the cortex or the columns of Bertin (10), both of these tissues having a different embryonal origin from the medulla. It was pointed out by GÜNTHER (17) in 1948 that two forms of the necrosis could be observed: medullary, centrally located in the papilla and papillary involving the whole papilla or sometimes nearly the whole pyramid. The changes may be found in one or more papillae and in one or, in most cases, both kidneys (17). The onset of the necrosis is rapid after which is a leukocytic demarcation, this finally leading to detachment (16). The lesion may subsequently heal, with epithelization (12, 17). The detached necrotic papilla tissue may either remain in the cavities formed, where it shrinks and is gradually resorbed, or it may be passed in the urine (12, 19). It may also form the nucleus of a concre-

tion (8, 13, 15 and 35). MANDEL and POPPER (1951) found in animal experiments that the necrotic papilla is sometimes not detached but undergoes fibrosis (22).

The radiologically observable changes were first described by PRAETORIUS in 1937 (27), and more recently in greater detail by GÜNTHER (16, 17). In the case of the medullary form a cavity is seen in the apex of the papilla, while the fornix of the calyx remains intact for a long time (Fig. 6). In the papillary form there is a typical ring shadow when the papilla has been detached (Fig. 1). When it has been resorbed or passed, a cavity with a wide base is formed (Figs. 2 and 4).

The typical radiologic features are not evident until the detachment has begun and the contrast medium enters the necrotic areas. The boundaries of the cavities are at first ragged, but after epithelization of the lesion they are smooth (17). Some authors have regarded enlargement of the kidneys as a typical roentgenologic feature (26, 37).

It is generally considered that the lesion of the papillae, of which the blood supply is poor in comparison with the rest of the kidney (24, 33, 35), is an ischaemic infarct (32). The mechanism of the development of these lesions has still not been established although a number of theories have been advanced.

We have made an attempt to collect the factors which have been regarded as promoting papillary necrosis. Any of the following disorders — except renal and intrarenal thrombosis or embolus in the vessels, cardiac insufficiency, allergic reactions and intoxications by, for instance, hypnotics and analgesics — is considered to be accompanied by infection of the urinary tract.

1. *Primary vascular changes in the kidney:*

   Renal and intrarenal thrombosis or embolus in the vessels (33, 35);
   Arterial and arteriolar sclerosis (10, 15);
   Intercapillary glomerulosclerosis (10, 14);
   Vascular spasm (3, 32);
   Vasoparalysis with multiple thrombi (17, 22);
   Periarteritis nodosa (37).

2. *Pressure on the papillary vessels by:*

   Inflammatory infiltrate or oedema (24, 31);
   Deposits of paramyloid (23);
   Contractions in the muscles around the papilla (3, 32);
   Stasis in the minor calyx due to constriction of its neck (28);
   Raised intrapelvic pressure (12, 24);
   Accumulation of small abscesses at the base of the papilla (31);
   Pyelo-venous or pyelo-tubular reflux of urine (10) and, in pyelography, reflux of contrast medium and infected urine (11).

3. *Cardiac insufficiency* (3, 33).

4. *Toxic impairment of the tissue by*:

   Bacterial toxins (16, 19);
   Intoxications by, for instance, hypnotics (18) and analgesics (34).

5. *Allergic reactions.*

Necrosis has been produced in animal experiments by the injection of vinylamine (22), tetra-hydroquinoline (29) and bromethylamine bromhydrate (25), as well as by diphtherotoxin (17) and bacteria (20). Necrosis has also been produced by ligation of the ureter in the dog and rabbit (24, 35) and by feeding the rat on a fat-free diet (4).

A study of the literature thus suggests that urinary tract infection is generally held to be an essential factor in papillary necrosis. In some subjects infection gives rise to a local reaction in the renal papillae, possibly through a disturbance of the circulation, as a result of which rapidly progressing necrosis occurs in an area that is demarcated from the surrounding renal tissue by a zone of leukocytes, the papilla being subsequently detached. Papillary necrosis with no demonstrable urinary tract infection rarely seems to occur.

Material

During the period 1952 to 1957 a total of 52 cases of renal papillary necrosis were examined roentgenologically in our department. One patient was treated in the Department of Urology without immediate previous roentgen examination, a satisfactory examination having been performed at the hospital from which the patient had been referred. In another case roentgenograms from another hospital were studied without the patient being treated. In one acute case the condition of the patient was too serious for urograms to be obtained, the diagnosis being made on autopsy.

The series thus consists of a total of 55 cases, with a sex distribution of 52 females to 3 males. The age at the establishment of roentgenologic changes ranged from 16 to 65 years, with a mean age of 43 years.

Only 6 patients (11 per cent) had diabetes, all of them women. In no case was there urinary tract obstruction.

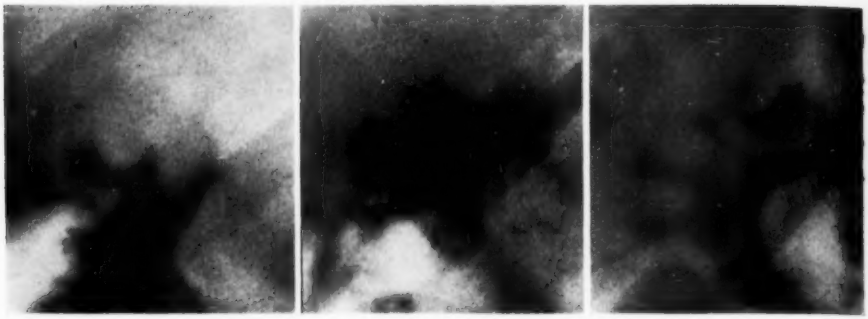
According to the roentgenograms and the autopsy examinations, the papillary changes were bilateral in 50 cases and unilateral in 5. The necrosis was purely papillary in 24 cases, medullary in 12, and both papillary and medullary in 18.

a b c

Fig. 1. Case 1. a) Normal urography. b) 8 months later. Cavities in several papillae and incipient detachment of papilla in upper minor calyx. c) 2 months later. Complete detachment of upper papilla: 'ring shadow'.

In 21 of the 55 cases (38 per cent), the secondary formation of calculus was observed: bilaterally in 14 and unilaterally in 7. The papillary form of necrosis was more common among these than among the cases in which there was no calculus. Among the calculus cases, *B. proteus* infection was predominant and, in the other cases, *E. coli*, although a number of other bacteria were also represented. The microstructure of the calculi in 8 of these cases was studied (Figs. 3 c, 5, 7, 9 and 11 c).

Clinical data. The histories of the 55 patients revealed an acute fulminating course in only two: a few were sub-acute and the remainder chronic. All but one of the patients had at some time during the course of the disease experienced symptom of urinary tract infection. The 2 acute and 36 chronic cases presented a clinical picture that earlier authors have regarded as typical (17, 23), viz. acute episodes with pain in the lumbar region, sometimes referred to the bladder, and accompanied by haematuria, leukocytosis, fever, chills and reduced renal function. The other patients showed less specific symptoms and signs of urinary tract infection or they had actual renal colic with passage of stones. In 5 cases there was continuous severe pain in the lumbar region, sometimes extending forwards to the abdomen and often unaccompanied by haematuria or high temperature. The pain, which resembled that occurring in vascular spasm diseases, was so severe and persistent in 2 cases that denervation of the kidney was considered, and in 1 of the cases actually performed. One of the patients had previously undergone sympathectomy for vascular

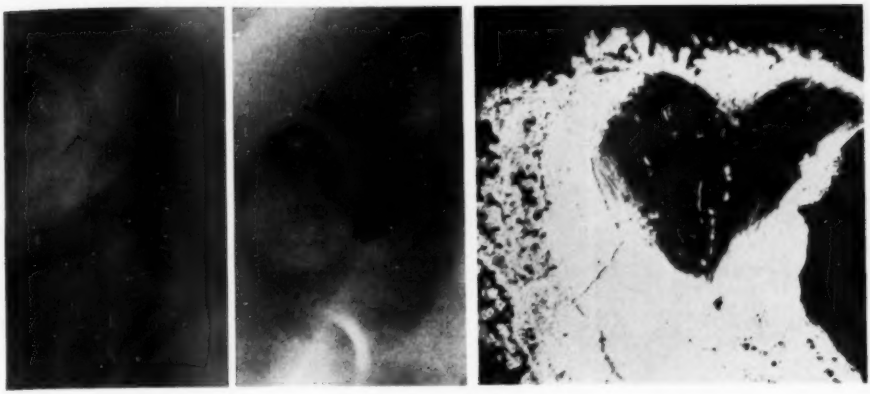


a b c

Fig. 2. Case 2. a) Typical papillitic changes in some papillae. Upper papilla normal. No calculus in conventional films. b) 6 months later. Upper papilla detached. c) 6 weeks later. Detached papilla still lying in cavity but now forming a concretion (Cf. fig. 3 b).

spasm in the legs. Prior to the appearance of the characteristic features 25 of the patients presenting the classical morbid picture had had atypical infections of the urinary tract lasting from a few weeks to 20 years. During the acute episode there was often reduced kidney function and an elevated non-protein nitrogen level. In the remissions the function was remarkably good, even normal values being found in 3 cases where inulin and creatinine clearance tests were performed. In the chronic cases, however, an irreversible reduction in the function of the kidney gradually set in, with hypertonia and anemia. Five of the 6 cases with fatal termination died of renal insufficiency. A few of the cases could be followed for periods of up to 10 years after diagnosis. In 2 of these the roentgenologic and clinical signs progressed only very slightly, suggesting a stabilization of the process.

In 6 cases typical clinical signs of papillary necrosis were observed over 1 to 4 years, with no evidence of abnormal changes in the urograms. Then, between two examinations, there was a sudden detachment of some or all of the papillae, the clinical picture remaining unaltered. In 1 of these cases, typical attacks of right renal colic accompanied by fever, chills and haematuria were experienced, but no stones passed. A year later similar signs appeared on the left side; there was a local destruction of the papillae of the left kidney while the right appeared to be normal. Left hemi-nephrectomy was performed, after which there were episodes predominantly on the right side. After three years there was still no urographic evidence of a pathologic condition of the right kidney. At the next urographic control a year later all the papillae of the right kidney had been detached, but there was no change in the clinical picture.



a b c

Fig. 3. Case 2. a) Conventional film from the same investigation as fig. 2 b. Superficial calcium incrustation of detached papilla. b) Conventional film at same time as fig. 2 c. Detached papilla now forms a calculus with a nucleus of low density and surrounded by dense shell of calcium salts, typical of papillary necrosis. c) Microradiogram of a 200 micra thick section of removed calculus, showing central papillary fragment.

Where nephrectomy is to be performed it is evidently impossible to exclude papillary changes in the other kidney solely from the roentgenograms; selective clearance tests should also be performed (9). On the other hand, typical necrosis in both the medullary and papillary forms developed during the period of observation in 4 cases, and the papillae were detached without the so-called 'typical' signs appearing — even long afterwards — the clinical picture being just one of ordinary non-complicated pyelitis or pyelonephritis. Some typical cases are described below.

Illustrative cases

Case 1 (Fig. 1). Woman, 35 years, with history of pulmonary tuberculosis and spondylitis tuberculosa. Since 1943 recurrent pain on the right side of the abdomen suggestive of renal calculus. Since May 1956 recurrent pyelitis with fever, chills, and microscopic haematuria. No diabetes.

Urography in May 1956 (Fig. 1 a) showed normal conditions but in February 1957 (Fig. 1 b) that the concentration capacity of the right kidney was somewhat diminished; there was slight shrinkage of the kidney, cavities in several papillae, and incipient detachment of the papilla of the upper minor calyx. *E. coli* was found in the urine but no evidence of tuberculosis. Urography in April 1957 (Fig. 1 c) showed further reduced concentration capacity with increased shrinkage of the kidney. Complete detachment of the uppermost papilla with 'ring shadow'. In May 1957: right nephrectomy. Histologic examination: renal papillary necrosis.

a b c

Fig. 4. Case 3. a) Normal urography. b) 4 years later. Extensive necrosis of papillary type with calcareous incrustation of detached papillae. c) Conventional film from same investigation showing typical calculi in kidney.

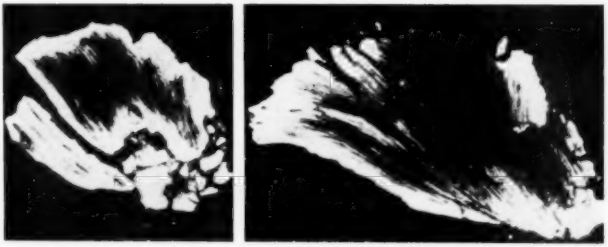
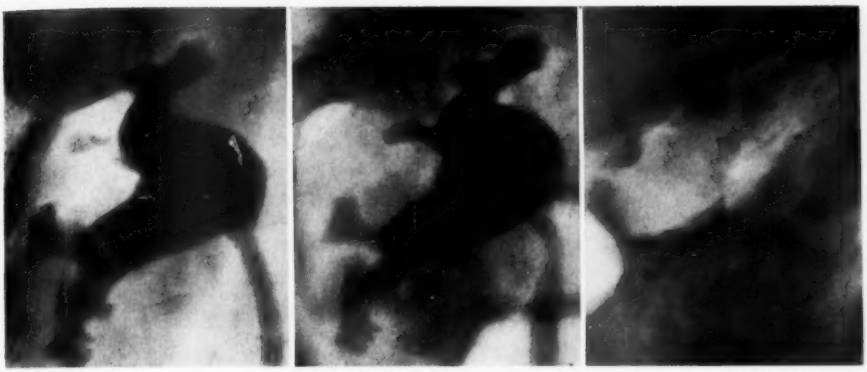


Fig. 5. Case 3. Microradiogram of 250 micra thick sections of calculi removed from right ureter, demonstrating papillary fragments with accretion of calcareous material.

Case 2 (Figs. 2 and 3). Woman, 52 years. Healthy until the beginning of October 1955 when she became acutely ill with pain on left side suggestive of renal calculus together with fever, chills, and microscopic haematuria. Anemia. S. R. and N. P. N. level elevated. A few days later necrotic papilla fragments passed, after which the symptoms abated. No diabetes.

Urography a few days later (Fig. 2 a) showed typical papillitic changes in some papillae of both kidneys. Recurrent symptoms and signs thereafter referable to both kidneys. At first there were no bacteria in the urine but since 1956 *B. proteus* was found. Urography, April 1956 (Figs. 2 b and 3 a) showed incipient superficial incrustation of some detached



a b c

Fig. 6. Case 4. a) Changes of medullary type in all papillae. No calculus visible in conventional films. b) 9½ years later. No appreciable change. c) Conventional film at same time as (b) showing several small calculi in the cavities.

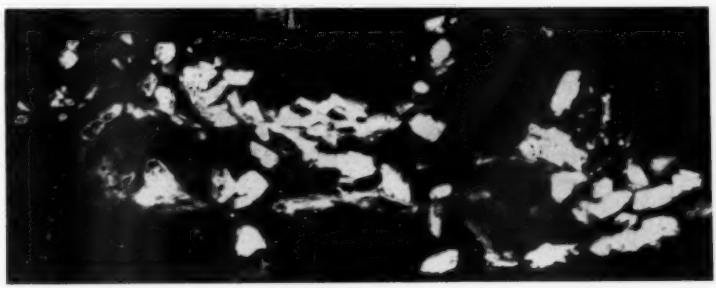


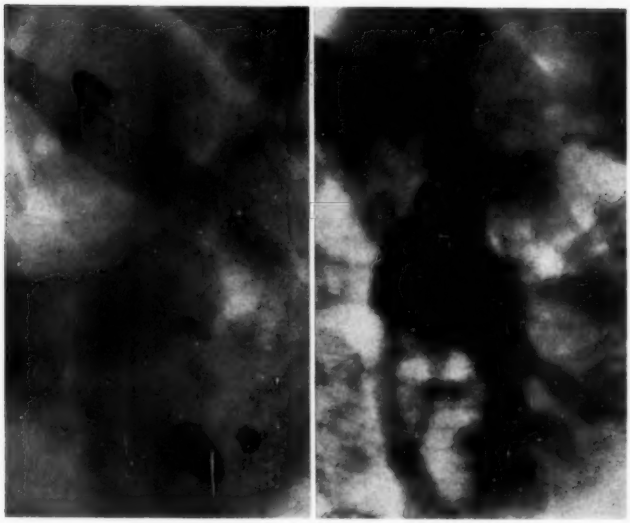
Fig. 7. Case 4. Microradiogram of a 200 micra thick section of one of the calculi seen in fig. 6 c, showing distinct tubular structures.

papillae. Urography, June 1956 (Figs. 2 c and 3 b) revealed that the detached papillae had formed renal calculus typical of papillary necrosis, with a radiolucent nucleus and a dense shell.

Microradiograms of removed calculus confirmed papillary structure (Fig. 3 c).

Case 3 (Figs. 4 and 5). Woman, 40 years, with recurrent pain generally radiating to the abdomen since 1952. On one occasion slight fever and slightly elevated S. R. Partial gastrectomy 1952 for duodenal ulcer. No bacteria in the urine. No diabetes.

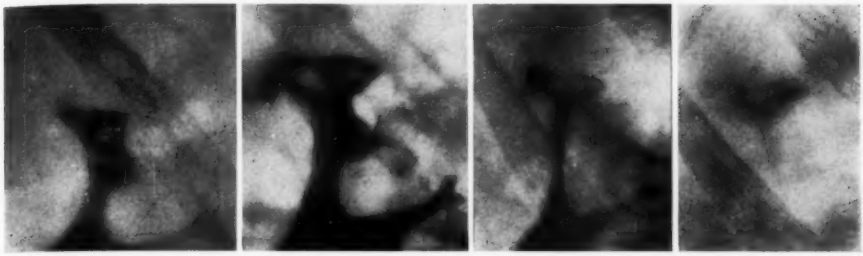
Urography, November 1952 (Fig. 4 a), showed nothing abnormal. No signs referable to urinary tract until 1955 when on one occasion there was silent haematuria. Since November 1956 recurrent pain on both sides suggestive of renal calculus; haematuria but no fever. S. R. and N. P. N. level normal. Admitted in November the same year



a b

Fig. 8. Case 5. Changes of papillary type with accretion of calcareous material on several detached papillae, lying free in the cavities.

Fig. 9. Case 5. Microradiogram of 180 micra thick sections of two removed calculi containing papillary fragments.



a b c d

Fig. 10. Case 6. a) Normal urography. b) 13 months later. Upper papilla detached and lying free in cavity, but in conventional films no accretion of calcareous material visible. c) and d) A further 13 months later. The detached papilla now shows incrustation.

with a diagnosis of nephrocalcinosis. Urography: extensive necrosis of papillary type in both kidneys, and calcareous incrustation of the detached papillae (Fig. 4, b and c).

Microradiograms of removed calculus: typical papillary structures (Fig. 5).

Case 4 (Figs. 6 and 7). Woman, aged 60. After several years of mild attacks of pain suggestive of renal calculus, in January 1947 a severe attack on the left side was accompanied by fever, urgency, and haematuria. Nine days later a necrotic papilla fragment was passed. Hypertonia since 1948. No bacteria in the urine. No diabetes.

Urography two weeks later (Fig. 6 a): typical changes of the medullary type in both kidneys. After that there were bilateral symptoms of varying severity until 1951, since when they had been only mild. N. P. N. level normal. Urography in 1956 (Fig. 6, b and c) showed several small calculi in the cavities but otherwise the same appearances as in 1947.

The patient died of subarachnoid haemorrhage following gastrectomy in November 1956. Post-mortem examination of the kidneys: renal papillary necrosis.

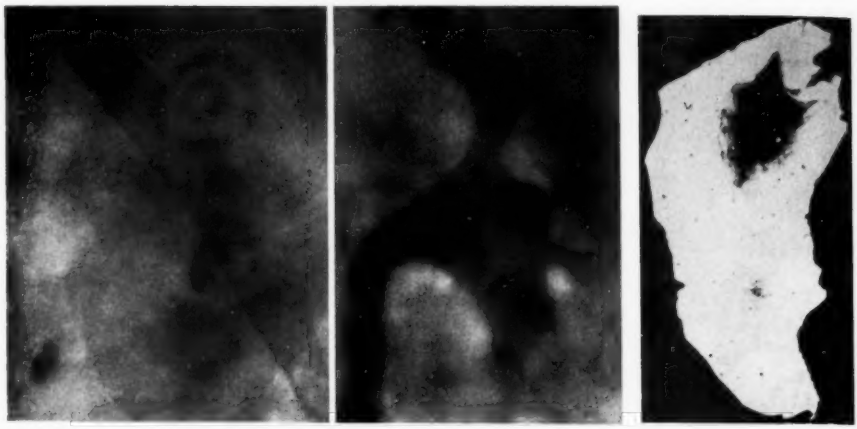
Case 5 (Figs. 8 and 9). Woman, 48 years. Since 1941 recurrent pain in the lumbar region often accompanied by fever, urgency and haematuria. Hypertonia since 1942. No diabetes. Operation 1951 for suspected hyperparathyreoidism, a hyperplastic parathyroid gland being removed. No bacteria in the urine from 1949 to 1954. Since 1956 *E. coli* infection and since 1957 *B. proteus*.

Urographies (Fig. 8) showed changes of the papillary type with calcareous material on the detached papillae.

Microradiography of removed calculus: typical papillary structures in the nucleus (Fig. 9).

Case 6 (Fig. 10). Woman, 59 years. One attack of left-sided renal pain in 1950. Since September 1955 bilateral recurrent cystopyelitis attacks with aching in the lumbar region, urgency and fever, but no frank haematuria. *B. proteus* was found. No diabetes.

Urography in January 1955 (Fig. 10 a) showed normal appearances. S. R. and N. P. N. level normal. Pyelography (Fig. 10 b) and urography in February 1956 showed total detachment of uppermost papilla of the left kidney, but no calculus. In April 1956 clearance revealed a decrease of the renal function to about 30 per cent of normal. Uro-



a b c

Fig. 11. Case 7. a) and b) Calculus with non-dense nucleus suggestive of papillary necrosis at lower pole of left kidney. (Concrement in the ureter.) c) Microradiogram of a 200 micra thick section of the voided calculus with tubular tissue at the centre.

graphy in March 1957 (Fig. 10, c and d) showed that the detached papilla had been incrustated with calcareous material. The kidney had shrunk and its concentration capacity was diminished.

Case 7 (Fig. 11). Man, aged 48. Ulcerative colitis from 1942 to 1953. Since 1954 recurrent renal colic with passage of calculi but no evidence of infection. No diabetes.

Urography, January 1957 (Fig. 11, a and b) showed a calculus in the lower pole of the left kidney, suggestive of papillary necrosis because of the non-dense nucleus.

Microradiogram of the passed calculus showed typical tubular tissue at the centre (Fig. 11 c).

Roentgenologic findings

Scrutiny of the roentgenograms led to the conclusion that with the authors' present experience the diagnosis could undoubtedly have been made primarily from these in 48 of 54 cases: 46 of which were urographies and 2 pyelographies. In 4 cases, papillary fragments had been passed with the urine before an examination could be performed, but the subsequent study revealed typical changes, in 3 cases by urography and in one case by pyelography. In one case, no papillary changes could be observed in spite of a careful urographic examination. In another case, a calculus situated in a calyx and suggestive of papillary necrosis was analyzed when it was passed and found to contain papillary tissue (Fig. 11 c). With one case the condition followed a fairly acute course in one

kidney. Urograms taken one month after the symptoms had appeared showed no excretion on the diseased side and no abnormality at pyelography. After nephrectomy necrosis was found in all the papillae, but there was still no detachment, a fact that explains the negative roentgenographic findings. Typical changes were subsequently found in the other kidney, the disease then assuming a more chronic course.

There were thus typical roentgen appearances in 52 of the 54 cases examined. Pyelography was performed only in cases in which the function of the kidney was reduced to such an extent that urograms would not have provided sufficient information.

The roentgen diagnosis was confirmed in 20 cases by biopsy — by examination of passed papilla fragments in 7 cases, by microradiography of calculi in 6, by autopsy in 3, and by examination of the removed kidney in 4 cases.

The roentgenologic differential diagnosis. The conditions to be borne in mind when making a differential diagnosis are renal tuberculosis, pyelonephritis without papillary necrosis, hypoplasia, calyceal diverticula, 'medullary spongy kidney', and reflux in connection with a retrograde examination. Where there is a concretion, other similar calculus conditions and nephrocalcinosis, etc., must be ruled out.

In the early stage there may be difficulty in distinguishing papillitis from *renal tuberculosis*, especially if the case is one of local renal papillary necrosis (10). Before detachment is complete it is possible to see only a contrast reflux in the parenchyma, and the appearances may closely resemble those presented by incipient tuberculosis. However, the subsequent development with for instance, stricture of the calyx neck or destruction of the parenchyma in the case of tuberculosis, soon indicates the correct diagnosis. The cavities in the papillae differ from those occurring in tuberculosis; in the urographic examination the former immediately fill with contrast medium. The changes are restricted to the actual papillae and are not found in the peripheral parenchyma as in the case of tuberculosis. Improvement in function after the abatement of the symptoms does not occur to the same extent in tuberculosis as in the periods of remission in papillitis. In aortography, which must now be considered as contraindicated in renal papillary necrosis owing to the risk of further damage to the kidney there is, unlike in renal tuberculosis, an apparently normal accumulation of contrast medium in the kidney. Tests for tuberculosis should, however, always be performed in doubtful cases.

A shrunken kidney in *pyelonephritis* may closely resemble a similar condition due to papillary necrosis. In the former the calyces are club-shaped but there is no detachment of the papillae. The typical acute episodes are also absent.

The cavities of *hypoplasia* as seen in the roentgenograms, may resemble those noted on healing of the process in papillary necrosis. The criterium of hypoplasia of the kidney is that both the medullary substance and the cortex are underdeveloped; in the case of papillitic cavities there is no hypoplasia of the cortex. The correct diagnosis will be clear from the subsequent development of the disease.

Calyceal diverticula should not be confused with papillitic cavities, since the former are connected with the fornix of the calyx and extend upwards between the pyramids, whereas the latter are formed in the actual papilla.

The '*medullary spongy kidney*' has a characteristic roentgen picture, and the course of the disease is quite distinct from that of papillary necrosis. 'Spongy kidney' is looked upon as a congenital deformation of the tubules in the papillae or fairly large parts of the medullary substance, with cystic dilation of the tubules. The course of the disease is primarily symptomless but stones are often formed secondarily in these cavities, which may then present the typical symptoms of renal calculi (5). The papillae in the 'spongy kidney' are generally larger than normally, and where the condition is generalized the whole kidney is enlarged. The function of the kidney is always normal. Urinary tract infection only now and then complicates the disease. Roentgen examination reveals multiple, round, oval or cylindrical cavities in the papillae or in the medullary substance nearly up to the border of the cortex and the medulla, but never actually in the cortex. In urography these cavities, like the papillitic cavities, are immediately filled with contrast medium (LINDVALL).

Urinary calculi in papillary necrosis

In infections of the urinary tract there is always a greater tendency towards the formation of calculi, one reason for which is that certain strains of bacteria alter the physical properties of the urine and provide a more favourable environment for the precipitation of salts normally occurring in the urine. It is therefore to be expected that some patients with papillary necrosis may also have calculi in the urinary tract. In fact this was observed in the films of no less than 21 of the 55 cases (38 per cent). Even when account is taken of the many patients who had had chronic pyelitis and cystitis over long periods — conditions that themselves favour the formation of calculi — this percentage must be considered as high. One explanation is that the necrotic papilla fragments on detachment form nuclei for the accretion of salts. The periodic course of the disease, with reduced renal function in the acute episodes followed by relatively good function in the periods of remission, may also favour the formation of calculi. It is probable that a certain residual

function of the kidneys is necessary for the salts to be excreted in sufficiently high concentrations for the production of calculi, and the temporary rise in excretion accompanying the improvement in function is of significance. Since cases of papillary necrosis with a longstanding infection of the urinary tract present conditions which favour the rapid accretion of calcareous material around the papilla fragments, the calculus, which would otherwise further reduce the renal function, should be removed surgically when all the papillae have been destroyed and the risk of the recurrence of calculi has thus been reduced.

In order to demonstrate that the nucleus of removed stones was really composed of papilla fragments, 8 of the 21 cases were studied by microradiography and the chemical composition was determined by roentgen crystallography (Figs. 3 c, 5, 7, 9 and 11 c). In all 8 cases papilla fragments were found in one or more calculi and in 2 of these there were also calculi without such nuclei. In the other 13 cases the calculus had been formed during the period of the disease, and in appearance closely resembled the microradiographed specimens. It was thus concluded that these, too, were formed around papilla fragments. There was a somewhat irregular nucleus, in the centre of the concretion itself not dense but enclosed by the accreted salts (Figs. 3, 8 and 10). At an early stage these form only a thin skin, but the covering gradually thickens to become so dense as to conceal the nucleus entirely. The only calculus that could be confused with the typical papillitic stones are those with a nucleus of blood coagulate, which might also appear in papillary necrosis; there is often marked haematuria when the papilla is detached. Stones with a central rarefaction in combination with other suggestive roentgen features will support the diagnosis. As mentioned above, the diagnosis in one case was borne out by microradiographic study of a calculus, the appearance of which was suggestive of papillary necrosis, though no other roentgen changes were found (Fig 11).

Crystallographic analysis has shown that of the specimens of calculus from these 8 cases, 5 contained the mixture of ammonium magnesium phosphate and basic calcium phosphate typical of calculi formed in infections; 2 consisted only of basic calcium phosphate and in the remaining 1 from a case with no urinary tract infection the only inorganic material was calcium oxylate monohydrate.

The urinary calculi were studied by the biophysical methods described by LAGERGREN (21). They were first embedded in methyl methacrylate and, after polymerization, cut into thin slabs which were ground to sections of between 100 and 300 microns. The structure of these thin specimens was determined by microradiography, which revealed the distribution of the mineral salts by virtue of their characteristic density.

The chemical composition of the small structures seen in the microradiogram was determined by means of an accurate X-ray microcrystallographic technique.

Discussion

Of the 54 cases of the present material in which urography or pyelography was performed there were typical appearances in 52. These means of investigation are very important, as without them it is impossible to make more than a presumptive diagnosis unless an examination can be made of papilla fragments passed in the urine or removed surgically. Earlier workers have regarded it as very difficult to make a diagnosis by roentgenographic means. Moreover, it has generally been maintained that urograms are difficult to interpret in cases of papillary necrosis owing to the reduced renal function; pyelography has been preferred to urography (15, 26). Pyelography is, however, used with restraint in our department especially when infection of the urinary tract is present, in order not to aggravate the condition. According to WALL (1954) the diagnosis had up to that time been made with the aid of roentgen rays in only 11 cases (37). GARRET, NORRIS & VELLIOS in 1954 considered that roentgenography "is helpful but not diagnostic" (14), and CHRISTOFFERSEN & ANDERSEN in 1956 and ANDERSEN in 1957 state that the roentgen diagnosis of papillary necrosis is difficult and often impossible (1, 6).

In the case material of this study it has been impossible to find any features other than those described in 1937 and 1948 by GÜNTHER as typical and those changes which are considered to be characteristic of pyelonephritis (28). An enlarged kidney was previously regarded as usual, whereas in most cases of the present series a more or less rapid shrinkage of the kidney was recorded. In sub-acute cases this may occur so quickly that measurable changes in size may be noted in as short a period as one month. This discrepancy is clearly due to the fact that in earlier times only acute cases, where the kidney would probably be enlarged, came to the notice of the physician, whereas the cases of the present series were of a chronic nature. The reason for the more frequent diagnosis of the disease by roentgenology must lie in the sub-acute and chronic course of the disease and enlarged experience, improved roentgen techniques, and better contrast media, which are effective in spite of reduced renal function. In one of the cases, for instance, satisfactory urograms were obtained where a clearance examination showed that both the filtration and tubular excretion were reduced by 70 per cent. According to studies by EDLING and co-workers (9), this may be ascribed to the fact that the urographic examination is a qualitative test of function. In spite of marked local destruction, the residual functional paren-

chyma may still, to judge from the films, provide a high urine concentration, although this is in fact not the case. On the other hand, the clearance test is quantitative and provides a better index of true renal function. In most of the cases where the clearance examination was performed, a reduced function was noted also in the free interval, while the non-protein nitrogen over the same periods was generally normal right up to the final stage.

In the sub-acute and chronic cases of papillary necrosis renal function in the acute episodes is often so seriously impaired that urograms are useless. In the intervening calmer periods the kidney recovers its function, though this is gradually reduced as the process continues. It is especially typical of papillary necrosis that a series of urograms will on one occasion disclose considerably reduced concentration capacity whereas on others a normal state is recorded. This variability is due to the fact that in the acute episodes, arising through acute papillary necrosis, there is a sudden flare-up of the infection accompanied by reduced renal function (17). When the necrotic portion is detached the infection recedes and there is a marked improvement in the function which may even become normal. In ordinary chronic pyelonephritis, however, there is a progressively slow reduction of renal function, or after a time the condition may become stabilized, but there is never any improvement.

In the early stages, before detachment has occurred, a perfectly normal roentgenogram, except for changes due to pyelitis or pyelonephritis, is obtained. Even when detachment has begun it may be difficult to interpret the findings, especially in the case of local papillary necrosis. When the necrotic portion has become detached a defective papilla is seen in the film, and as almost invariably several papillae are attacked typical appearances are eventually obtained. When papillary necrosis is suspected on clinical grounds and the first urography has proved negative, further examinations should be carried out, as papillary necrosis ultimately always presents typical changes. In the present case material the changes were generally observed in both kidneys, only 5 instances of a unilateral occurrence being found. When the disease has advanced so far that there are changes in several papillae of one or both kidneys, the roentgen findings are so characteristic that in combination with the clinical data the possibility of confusion with other renal conditions does not arise.

Only some 11 per cent of the patients had diabetes mellitus; this is a remarkably low figure compared with earlier experiences. THOMSEN-PEDERSEN stated in 1957, however, that diabetes occurred in only 15 per cent of the cases of his material (36), and SIMON, BENNETT and EMMETT had 19 per cent (33).

This case material differs from earlier ones in both the sex and age distributions. There are only 3 males, which fact is probably explained by the absence of any case of urinary tract obstruction.

Renal papillary necrosis occurs at all ages. The mean age at diagnosis in previous material has been 50 years (36), whereas in the present series it was a little over 40. This displacement in the age distribution is due to the fact that the diagnosis of the disease can to-day be made at a fairly early stage, instead of at post-mortem examinations as was formerly the case. ANDERSEN pointed out in 1957 that in rare cases a milder form of renal papillary necrosis is known for which the prognosis is more favourable, especially in young women (1).

Conclusions

Renal papillary necrosis is considerably more common than was formerly thought to be the case; in recent years it would seem to have changed in character, becoming more benign, with some change in the symptomatic picture. In practically all cases it occurs in combination with urinary tract infection, and principally in younger subjects, particularly women. There is no pathogenetic connection with diabetes mellitus or urinary tract obstruction.

The condition is complicated to a considerable degree by urinary calculi, of which the detached necrotic papilla fragments often form the nuclei. This may be demonstrated by microradiographic examination.

In the vast majority of cases the diagnosis can now be made antemortem at urography or pyelography; this is important as a clinical diagnosis is otherwise possible only by examination of papillary fragments obtained from the urine or by surgical removal.

SUMMARY

The paper provides an account of the follow-up of 55 cases of renal papillary necrosis. The value of the roentgenologic investigation, especially in the forms of urography and pyelography is stressed and the development of the characteristic changes is described. Special attention is paid to the formation of urinary calculi upon papillary fragments. A brief review of the clinical picture is given, and the pathogenetic problems are discussed.

ZUSAMMENFASSUNG

Ein Bericht über die Nachuntersuchungen von 55 Fällen mit Nekrose der Nierenpapillen wird abgegeben. Der Wert der Röntgenuntersuchung, besonders in Form einer Urographie oder Pyelographie, wird betont und die Entwicklung der charakteristischen Veränderungen beschrieben. Besondere Aufmerksamkeit wird der Bildung von Harnsteinen auf papillären Fragmenten gewidmet. Ein kurzer Überblick über das klinische Bild wird gegeben und die pathogenetischen Probleme werden besprochen.

RÉSUMÉ

Ce travail rend compte de l'évolution de 55 cas de nécrose des papilles rénales. Les auteurs soulignent la valeur de l'examen radiographique, en particulier de l'urographie et de la pyélographie, et ils décrivent l'évolution des lésions caractéristiques. Ils se sont particulièrement intéressés à la formation de calculs urinaires sur des fragments papillaires. Ils rappellent brièvement les tableaux cliniques et discutent les problèmes pathogéniques.

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BONE AND JOINT CHANGES IN HAEMOPHILIACS

by

Gabriel Stiris

The first account of bone changes in haemophiliacs was published in 1892 by KÖNIG, who classified them in three stages, viz. the haemarthrotic, the panarthritic, and the regressive.

Swelling of the joints, with pain and reduced mobility, is a prominent feature of the haemarthrotic stage. Changes in the synovial membranes, joint capsules, cartilages, and juxta-articular areas of the bone, occur in the panarthritic stage. The regressive stage consists of increasing deformity of the joints and rigidity associated with the development of contractures.

FONIO published an account of the development of the pathoanatomic changes. The initial haemarthrosis causes elevation of the intra-articular pressure, due to which the haematoma will attack the margin of the cartilage and penetrate towards the marrow space, thus causing erosion. An organized haematoma without particularly increased pressure may also cause erosion, as observed in subperiosteal haemorrhages. Cysts in juxta-articular areas of bone are assumed to be caused by haemorrhage; the contents are reddish-brown, necrotic, and the wall contains hemosiderin.

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Fig. 1. Typical changes in a haemophilic joint. Deformed condyles with irregular articular contours. Pseudo-osteophytes and cysts. Increased density of soft tissues.

Own investigation

The present material comprises 35 cases which have been treated in Departments A and B of Internal Medicine. Thirty of these showed clinical signs of articular haemorrhage, while in 5 there was no evidence of joint changes. The youngest patient was 3 and the oldest 71 years of age. It was possible to determine the approximate age at which the initial haemarthrosis took place in 22 patients, the average approximate age being 7 years. In the material of LYON-SMITH haemarthrosis was present in 70 % of the patients prior to the age of 2 years. THOMAS found a history of articular symptoms in childhood in about 78 % of his material, while in the remainder the joints were affected somewhat later. In a series of 76 haemophiliacs, examined at The Mayo Clinic, 44 patients (58 %) showed definite signs of pathologic changes in the bones or joints. The average age was 17.3 years.

In the majority of patients in the present material the initial haemorrhage in a joint followed a fair degree of trauma. The haemorrhages subsequently recurred with the slightest sprain or twist. Haemorrhage also occurred in some cases without external influence.

In only 1 of the 30 cases with definite evidence of articular haemorrhages was only one joint affected. The remainder presented clinical or roentgenographic changes in two or more joints.

The knee joint was the most commonly affected, the elbow joint and the ankle joint in turn being then involved. Somewhat less fre-

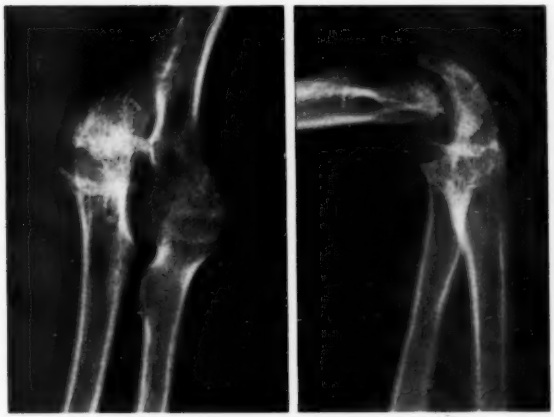

Fig. 2. Deformative changes in elbow joint of haemophiliac. Trochlea almost totally eroded, semilunar incisura widened and capitulum flattened. Small cysts in the juxta-articular parts of the humerus.

quently, haemorrhage was observed in the wrist, and rarely in the shoulder, hip, finger, and toe joints.

The haemorrhages were accompanied by swelling and intense pain in the joint, the patient being confined to bed for weeks up to months. Contracture with muscular atrophy usually developed. Articular changes have been observed at an early age. Three patients under ten years of age have shown changes in the joints with contracture and limited mobility. A total of 28 patients had clinical changes in one or more joints with deformity, malposition, contracture, and reduced mobility; there was also marked muscular atrophy.

A total number of 116 joints were examined roentgenographically in 27 patients, definite changes indicating haemophilia being demonstrated in 76 joints.

The most characteristic findings were erosion and cyst formation. The erosion generally occurs juxta-articularly, and the articular margin appears as a protrusion, a pseudo-deposit. This occurs most frequently in the knee and elbow joints and to a somewhat less degree in other joints. The erosion may be marked with some shrinkage in the articular cartilages. The natural depressions in the joints, such as the intercondyloid fossa in the knee joint and the semilunar incisura in the elbow joint, become wider and deeper (Figs. 1 to 4).

Cyst formation occurs in the majority of the joints. The cysts vary in size and are mainly situated in the epiphyseal area, although also

Fig. 3. Large cysts in the regions of metaphysis and epiphysis of femur; erosion and periosteal reaction along metaphysis. Smaller cysts in tibial condyles.

occurring in the metaphysis and diaphysis. In the affected knees of a boy aged 10 years, cysts the size of hen's eggs were situated mostly in the metaphyses of the femora as well as the tibiae, and were noted as breaking through the epiphyseal lines (Fig. 4 c). There were also large cortical defects, probably caused by erosion by subperiosteal haematomas; at the margin of these defects periosteal reaction appeared with external swelling of the soft tissues. Such changes could have been caused by a destructive malignant process. The bilateral almost symmetrical development, as well as the clinical findings, pointed, however, to haemophilic joints. Destructive changes were also found in the distal phalanges of the index finger of the left hand and in the right big toe (Fig. 4). The areas were surrounded by considerable swelling of the soft tissues. These changes have also been interpreted as sequelae to haemorrhage. In contrast with the other patients this boy showed a positive reaction to the tourniquet test.

Several authors have reported tumour-like changes in haemophiliacs (Becker, Firor & Woodhall, Echternacht, Reinecke & Wohlwill, Ghormley & Clegg). Petersen described a case of haemophilia with large bone cysts in the left iliac bone with myositis ossificans around the left hip joint.

Deformity is most frequently found in the knee and elbow joints, less frequently in the ankle joint and the other joints. The articular outlines are irregular with diminished articular space. Bony ankylosis

a b c

Fig. 4. Destructive changes in distal phalanx of: a) and b) left index finger, surrounded by soft tissue swelling; c) right big toe, surrounded by soft tissue swelling.

was demonstrated only once — in a knee joint. Contractures, however, frequently occurred. Hypertrophic joint capsules and increased density corresponding to the recesses were often observed. The increased density was assumed to have been caused by hemosiderin in the tissues. In some joints arthrotic changes were also observed in the regressive stage.

The differential diagnosis rarely presents any problems. The pseudo-marginal deposits are of decisive importance in differentiating the condition from arthrosis or chronic arthritis with osteophyte formation. Slight changes in the hip joint may simulate tuberculous coxitis; here the clinical examination will be helpful. Decalcification occurs relatively late in haemophilia (BUUS). When there is malposition of the femoral joint changes may be confused with congenital luxation of the hip. The femoral changes may also resemble Perthes' disease (coxa plana) or arthrosis, as mentioned by WINSTON. The majority of the patients were admitted to hospital for acute articular haemorrhages, and were treated with blood and plasma transfusions. Attempts were made to control contractures by traction or weighting. Surgery was not resorted to because of the risk of haemorrhage. The articular changes were generally accompanied by intense pain, which required medication. In some cases irradiation was employed, this usually bringing transitory relief from pain. The intra-articular injection of cortison was also tried with, however, doubtful effect.

Mac Ausland & Gartland described a method of treatment for acute haemarthrosis consisting of the intra-articular injections of hyaluronidase, which is an enzyme found among others, in the synovial fluid. This agent has the property of accelerating fluid resorption, as well as blood, from joints. They employed 1,000 units of hyaluronidase in 1 % procaine, and reported that the effect was evident within 24 hours. The dose may be repeated the following day if required.

Discussion

Without discussing in detail the mechanism of coagulation and the haematologic investigations which have been performed, a few facts may be mentioned. Haemophilia falls into two groups, A and B, the latter being considered to be more benign. Unfortunately only a few of the patients in the present material had been classified in groups. Both groups were represented, however, by patients with haemarthrosis; no difference in the articular changes has been demonstrated in the two groups. It appears to be the frequency and the degree of the haemorrhages which are decisive in the development of the articular changes.

As mentioned the haemorrhages may occur at an early age, even in the first year of life, and the trigger trauma may not necessarily be great. Frequently, however, the initial haemorrhage in our cases was provoked by a fair degree of trauma, while recurrence took place as a result of a slight sprain or twist, or the haemorrhages occurred without any external influence. The interval between the haemorrhages varied greatly. Uncommonly, however, the patients bled several times in the course of one year.

In all patients, except one, the tourniquet test was negative, thus indicating that there was no capillary brittleness. Still, it is remarkable that articular haemorrhages should occur more readily in haemophiliacs than in normal individuals, although it is understandable that the haemorrhage persists when it has once started. It does not seem plausible that haemophiliacs are more exposed to trauma than other individuals, particularly as they are bound to take every care of themselves. The possibility exists, of course, that the vessels in the joints and juxta-articular bone areas have somehow become brittle, although this is not confirmed by the tourniquet test. It is also possible that pathologic vessels are formed by a haemorrhage with organization of the haematoma. Herrlin makes similar suggestions. He states that it is difficult to understand why haemophiliacs so frequently bleed into the joints, and rarely in the central nervous system; furthermore, why articular haemorrhages are unusual when other plasma factors are absent, and why intracranial haemorrhages occur not infrequently, for example in thrombopenia. An analysis of local conditions of importance in haemostasis might perhaps offer some explanation.

SUMMARY

The author presents a survey of the changes occurring in bones and joints in a material of 35 haemophiliacs. The roentgen appearances are described and the differential diagnosis discussed. Attention is drawn to the incongruity between the negative tourniquet test and the tendency to haemorrhage in haemophiliacs. Various methods of treatment of the joints are mentioned.

ZUSAMMENFASSUNG

Der Verfasser gibt einen Überblick über die Veränderungen, welche in den Knochen und Gelenken in einem Material von 35 Hämophilen gefunden wurden. Das röntgenologische Aussehen wird beschrieben und die Differentialdiagnose diskutiert. Auf die Inkongruenz zwischen dem negativen Kompressionstest und der Blutungsneigung bei Hämophilen wird aufmerksam gemacht. Verschiedene Behandlungsmethoden der Gelenke werden erwähnt.

RÉSUMÉ

L'auteur décrit les lésions osseuses et articulaires observées sur une série de 35 hémophiles. Il décrit les aspects radiologiques et discute le diagnostic différentiel. Il attire l'attention sur la discordance entre le signe du lacet négatif et la tendance aux hémorragies des hémophiles. Il signale différentes méthodes de traitement des articulations.

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ROENTGENOLOGIC DEMONSTRATION OF RECURRENT TRACHEO-OESOPHAGEAL FISTULA FOLLOWING SURGICAL REPAIR OF CONGENITAL OESOPHAGEAL ATRESIA

by

C. E. Gudbjerg and *Tyge Cl. Gertz*

Since the surgical treatment of oesophageal atresia was introduced at our hospital about 10 years ago, 67 cases of this condition have been admitted to the Paediatric Department, 52 of these being subjected to radical operation. The introduction of surgical treatment has materially altered the prognosis, the mortality now being about 46 % against a previous 100 %.

The clinical and therapeutic details of the primary condition will not be discussed here; the reader is referred to a clinical paper on oesophageal atresia by GERTZ & WINKEL SMITH (1958).

In no small proportion of our cases an apparently smooth postoperative course was followed by a serious complication which so far does not appear to have received sufficient attention, viz. recurrence of the tracheo-oesophageal fistula.

We have not encountered cases of fistula without atresia similar to those described by SIEBER and GIRDANY (1956). As early as 1944, however, LADD reported 2 cases, both fatal. SHAW, PAULSON & SIEBER (1955) found recurrent fistula in 8 out of 54 cases following

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primary oesophageal anastomosis and SIEBER & GIRDANY reported 7 cases in 36 radical operations for oesophageal atresia.

In our series of 52 operated cases a recurrent fistula has been demonstrated with certainty in 10. In 3 of these cases the fistula was demonstrated at necropsy without any previous roentgenographic examination. Out of the remaining 7 (5 died and 2 were discharged in good health) the fistula was demonstrated roentgenographically in 4, whereas in 3 the examination produced a negative result. This is no doubt due to an alteration in the technique, the 4 positive cases being from the past year during which we have been using the special technique to be described below. Only once did this method fail to show the fistula. The remaining 2 negative cases were examined by the old technique, in which barium was employed.

In those cases in which the fistula was not diagnosed until after death, the clinical course had not suggested a recurrent fistula. All three patients died within the first two postoperative weeks, and the course was characterized by pulmonary complications. There is little doubt, however, that the recurrent fistula was an essential contributory factor.

In the remaining cases the symptoms and course were very much alike. The primary course was on the whole uneventful up to 3 months. Then, at a time when the risk of serious complications was believed to be over, the patients began to show respiratory distress associated with their feedings, indicating a flow of the oesophageal contents to the trachea and bronchi. When the presence of an oesophageal stricture could be ruled out by the passage of a gastric tube or roentgenographic examination, this could only be interpreted as evidence of a recurrent tracheo-oesophageal fistula. It has been valuable, however, to confirm the diagnosis roentgenographically as re-operation — the only possible treatment — is a hazardous undertaking to which we did not like to resort without being absolutely sure of the diagnosis.

The following are characteristic case histories:

Case 1. Female infant, aged 2 days, admitted with pneumonia. On the day after birth she had been slightly cyanosed, and roentgenography showed atelectasis of the right lung. An attempt to pass a catheter down the oesophagus revealed atresia. There was a large amount of gas in the stomach and intestines, suggesting a tracheo-oesophageal fistula. Radical operation was performed. The patient made an uneventful recovery but at the end of a few weeks developed dysphagia and attacks of cyanosis during her feedings. Roentgenography showed a recurrent tracheo-oesophageal fistula (Fig. 1).

The fistula was closed again through a thoracotomy incision but following the development of postoperative empyema, the condition of the patient deteriorated and she died 7 weeks after admission. Necropsy revealed a fine fistula from the trachea to the oesophagus, widespread atelectasis, and pneumonic changes in the lungs, as well as right-sided empyema.

Fig. 1.

Fig. 2.

Fig. 1. Recurrent tracheo-oesophageal fistula. Rounded accumulation of contrast medium between oesophagus and trachea representing an abscess cavity (confirmed at operation).

Fig. 2. Recurrent tracheo-oesophageal fistula following primary anastomosis of oesophagus and closure of original fistula.

Case 2. Female infant, aged 3 days. Twelve hours after birth, she had been admitted to a local hospital with attacks of cyanosis. Attempts to pass a catheter down the oesophagus and roentgenography of the lungs suggested atresia and right-sided pulmonary atelectasis. After radical operation, the postoperative course was uneventful. The patient was discharged 8 weeks after operation, but 3 weeks later was re-admitted with respiratory distress. At that time, roentgenography revealed confluent atelectases in the right lung as well as a tracheo-oesophageal fistula (Fig. 2). Further thoracotomy was performed, and the fistula was closed. The postoperative course was satisfactory, and at follow-up, 6 months after the final discharge, the patient was well-nourished and in good health; she was gaining weight, had no dysphagia, and roentgenography of the oesophagus showed only a slight retraction at the site of operation and negligible dilatation above it.

Technique

Although, as already mentioned, the diagnosis of recurrent fistula may be inferred from the clinical course, it is important that it should be confirmed prior to operation. To avoid the risk of filling the trachea with barium, we use the technique advocated by SIEBER & GIRDANY (1956).

After introducing a soft rubber catheter under fluoroscopic control, a bronchographic medium is cautiously injected. We use the aqueous solution of Dionosil. During this procedure, the presence of an anaesthetist is a safeguard so that suction may be performed in the event of any flow of contrast medium into the trachea. It is only when this can be avoided that filling of the trachea can be definitely taken to indicate the presence of a fistula. Under continued fluoroscopic control the patient is turned into various postures, films being obtained in the supine, prone, and both lateral positions.

Conclusion

Following operation for congenital oesophageal atresia some cases may, after an apparently uneventful postoperative recovery, develop clinical signs of recurrent tracheo-oesophageal fistula 2 weeks to 3 months after the operation. Re-operation is the only possible treatment, but since it involves considerable hazards, pre-operative roentgenographic confirmation of the diagnosis is of great importance. Roentgenography is carried out with a bronchographic contrast medium (Dionosil) introduced through an oesophageal catheter under fluoroscopic control.

SUMMARY

Out of 52 surgically treated cases of oesophageal atresia, 10 had a recurrence of tracheo-oesophageal fistula. In 3 instances, the diagnosis was confirmed at necropsy and in the others at re-operation. Seven patients were examined roentgenographically, in 5 of these by a special technique for demonstrating the fistula by the injection of Dionosil through a catheter. In 4 of these 5 cases the fistula was demonstrated roentgenographically before re-operation.

ZUSAMMENFASSUNG

In 10 von 52 chirurgisch behandelten Fällen mit Ösophagusatresie traten tracheo-ösophageale Rezidiv-Fisteln auf. In 3 Fällen wurde die Diagnose bei der Sektion bestätigt, in den übrigen bei der Reoperation. Sieben Patienten sind röntgenologisch untersucht worden, 5 von diesen mit einer Spezialtechnik zur Darstellung der Fistel nach Dionosil-injektion durch einen Katheter. In 4 von diesen 5 Fällen wurde die Fistel vor der Reoperation röntgenographisch demonstriert.

RÉSUMÉ

Sur 52 cas d'atrésie oesophagienne traités chirurgicalement, 10 ont présenté une fistule trachéo-oesophagienne récidivante. Dans trois cas, ce diagnostic a été confirmé à l'autopsie, dans les autres par la réintervention. Sept malades ont été radiographiés, dans 5 de ces cas par une technique spéciale pour mettre en évidence la fistule par injection de Dionosil par une sonde. Dans 4 de ces 5 cas, la fistule a été mise en évidence radiographiquement avant la réintervention.

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AN IMPROVED TECHNIQUE FOR TESTING THE EFFECT OF CONTRAST MEDIA AND OTHER SUBSTANCES ON THE BLOOD-BRAIN BARRIER

by

Oskar Steinwall

The ordinary method of testing the toxicity of substances by administering them intravenously or in some other way until they reach a certain concentration in the blood is generally unsuitable for assessing their toxic effect on the blood-brain barrier; the organism is often seriously intoxicated before the concentration which damages the barrier is reached. Furthermore, it often needs a great deal of work to determine the active concentration of the substance in the blood, which makes it difficult to work with large experimental series. A convenient way to test the barrier-damaging effect is to introduce a solution of the substance into a vascular region which is emptied of blood during the test. The exact active concentration is then known and there are no reactions between the blood and the substance, the effect of which may be hard to judge. It is true that ischemia damages the vessels, but it has been shown that when the vessels are emptied only for a few minutes the damage is insignificant in degree and constitutes a factor largely constant from test to test (2).

Broman and Olsson described a method based on these principles in 1948 and 1956 and also reported their procedure for demonstrating barrier damage with a vital dye test (3, 5). I used this method in rabbits

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and found that their technique could be improved by a simple modification; this will be described and an example of its effect on the test results given.

The method of BROMAN and OLSSON is briefly as follows. The solution to be tested is injected into the ligated common carotid artery in a cranial direction at a pressure which expels the blood from the vessels of the ipsilateral hemisphere as long as the fluid is being injected. This can be controlled by inspecting the pial vessels through a trephine opening.

In the rabbit (as in man) there is no rete mirabile caroticum and the hemisphere is supplied with carotid blood exclusively by the internal carotid artery (7). The injection is performed just below the origin of this fine vessel, which branches off at almost a right angle from the common carotid artery. As the external trunk is much larger, it takes up most of the carotid blood. Likewise, most of the solution injected flows out into the external branches and only a small amount goes to the brain via the internal carotid artery. In addition, the flow to the internal branch is apt to be impeded when the animal's head is twisted for inspection of the trephine opening over the hemisphere. In order to eliminate these disadvantages I ligate the external carotid artery directly cranial to the origin of the internal branch and likewise small vessels running to the neck from the internal artery or nearby parts of the common carotid artery. This forces all the injected fluid into the vessels of the hemisphere, and the injection can be performed much more slowly, and with only about one-tenth the amount of fluid, than when the external branches are patent. It also makes it easier to expel all the blood during the injection and to control the pressure of injection and the counter-pressure of the blood. Measurements of these pressures (with the Elema electromanometer and mingograph) in a number of experiments showed that the injection pressure keeps close enough to the pressure of the blood (though occasional transient differences of a larger order may occur) and that an experienced operator is unlikely to inject at a pressure that is so high as to affect the results.

In order to find out if my modification changed the test results previously obtained, I used it for studying the lowest barrier-damaging concentration of certain roentgen contrast media earlier studied by BROMAN and OLSSON (4, 6). Except for this modification I carried out the experiments in the same way as these authors so that our results for the concentration factor could be compared. Thus I used the same technique as they did for demonstrating barrier damage with intravenously administered trypan blue. (Barrier damage here means an impairment in the barrier mechanism which normally hinders trypan blue from passing from the blood out into the surrounding brain tissue.)

Table

		Concentration	Injection time (sec)	Number of experiments with	
				Barrier damaged	Barrier intact
DIODONE (Umbradil, Dijodon)	Own experiments	25 %	35	1	—
		20 %	20, 40, 40	3	—
		17½ %	40	2	—
		17½ %	20, 30	—	2
		15 %	20, 40	—	2
	BROMAN and OLSSON 1956	35 %	40	2	2
ACETRIZOATE (Reopak, Triurol)	Own experiments	20 %	25	1	—
		17½ %	30	1	—
		15 %	30, 30, 35, 40, 40, 45	6	—
		12½ %	40	1	1
		12½ %	45	1	—
	BROMAN and OLSSON 1956	25 %	40	1	1
			44	1 (?1)	

The accompanying table shows the lowest concentrations that caused damage as shown by the investigation of 1956 and by mine. It is seen that in my experiments barrier damage was obtained after much more dilute solutions of the contrast agents than those which produced alternatively positive and negative results in the previous experiments; the lowest concentrations causing barrier damage in my experiments were approximately half those of the corresponding limits of the authors mentioned. This was true of both Diodone and the acetrizoate media.

Conclusions

The main reason for the difference in our results seems to be that when the external carotid artery is ligated as described, there is less risk of distortion of the results by uncontrollable dilution of the injected fluid by blood. Obviously this modification ensures better defined conditions, an important requirement for comparative tests of this nature. It also makes it possible to produce conditions comparable to those used in cerebral angiography in man, in which the contrast medium is injected directly into the internal carotid artery.

SUMMARY

The author describes a modification of the experimental technique elaborated by BROMAN & OLSSON for studying the damaging effect of roentgen contrast media and other substances on the blood-brain barrier in the rabbit. The influence of this modification on the test results is discussed.

ZUSAMMENFASSUNG

Der Verfasser beschreibt eine Modifikation der von BROMAN und OLSSON ausgearbeiteten experimentellen Technik für das Studium der schädlichen Wirkung von Röntgenkontrastmitteln und anderen Substanzen auf die Blut-Hirnbarriäre des Kaninchens. Der Einfluss dieser Modifikation auf die Testresultate wird besprochen.

RÉSUMÉ

L'auteur décrit une modification de la technique expérimentale mise au point par BROMAN et OLSSON pour étudier les effects nocifs des produits de contraste radiologiques et d'autres substances sur la barrière sang-cerveau chez le lapin. Il examine l'influence de cette modification sur les résultats expérimentaux.

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DOSE DISTRIBUTION IN THE ROENTGEN TREATMENT OF TUMOURS OF THE CEREBRAL HEMISPHERES WITH MULTI-FIELD TECHNIQUE

by

Martin Lindgren

It was formerly the rule to use apparatus with kilo voltages of up to about 200 in the roentgen therapy of tumours. Deeply situated tumours were irradiated via several fields in order to increase the dosage delivered and in recent years the moving field technique has also been employed.

The multi-field technique has been widely used in the treatment of gliomas of the astrocytoma group (RINGERTZ 1950) in the cerebrum, especially when situated in one hemisphere. This technique has often been used in our Department of Therapy, mostly with 4 fields placed over the tumour region. The fields generally measured between 6×6 and 6×8 cm, the distance between the borders of adjacent fields being 5 to 7 mm and the skin dose per field treated 4,000 r, or somewhat less (LINDGREN 1953). Analysis of the material showed that the clinical course after radiotherapy often follows a certain pattern. The patients first felt better and some of them were able to return to work. Sooner or later, however, they deteriorated rapidly. This was more common after shortening of the treatment time (1952) from 60 to 80 days to 30 to 40 days with the same total skin dose. It is difficult to say whether this deterioration was due to cere-

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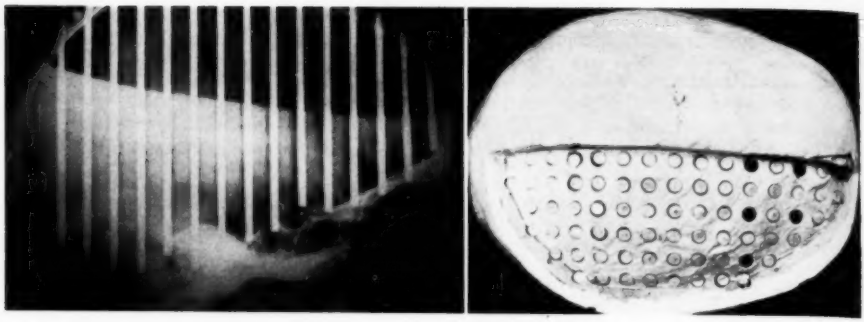

a b

Fig. 1. Roentgenograms showing arrangement of holes drilled in sawn sections of the skull and filled with Mix D. Some holes are not filled with the mix.

bral edema, hemorrhage, progression of the tumour growth, or cerebral necroses. Post-mortem examination of irradiated brain tissue showed changes suggesting overdosage in superficial regions of the brain with consequent tissue destruction. This prompted a systematic investigation of the three-dimensional distribution of the dose delivered by the technique.

I. Experimental measurement of the doses in a skull phantom

A. Measuring technique

A human cranium was used. The calotte was sawn along the sagittal plane and a plane parallel to that running horizontal through the auditory ducts and inferior orbital margins; the bone material lost was replaced by aluminium strips. Both the brain and the scalp were replaced by a tissue-equivalent material, Mix D, consisting of 60.8 % paraffin, 30.4 % polythene, 6.4 % magnesium oxide, and 2.4 % titanium oxide (JONES and RAINE 1949). A portion of the melted material was poured into the skull and allowed to settle in a layer about 0.5 cm thick. This was repeated several times until the skull was filled; by loading the skull in this way

cracking and sintring of the oxides was prevented. The soft tissues on the outer surface of the skull were replaced by a layer, about 0.5 cm thick, of the same material.

The intracranial doses were measured with cylindric ionisation chambers (see page 288) 20 mm long and 5 mm diameter. For this purpose, holes 5 mm in diameter and arranged according to a certain geometric system (Fig. 1a) through one half of the cranium were drilled to the base of the skull. The holes (Fig. 1b) were placed in 6 vertical planes parallel to the sagittal plane and perpendicular to the horizontal plane. The axes of the holes were spaced 10 mm apart.

Fig. 2. Fields, about 6×6 cm, situated 5 mm apart on skull phantom. Dotted line indicates horizontal plane at level of centre of tumour (L plane).

In order that the ionisation chambers could be placed ad libitum inside the skull, every hole was made to accommodate Mix D rods 5, 10, and 20 mm in length; by a suitable combination of the rods the ionisation chambers could be placed at the desired level in the cranium, the hollow space above the chamber being filled with pieces of rods up to the surface of the 'brain'.

After the phantom had been prepared in this way an imaginary tumour region in the anterior part of one of the hemispheres was selected for investigation and the fields and directions of the rays were adjusted to clinical conditions (Fig. 2). Four fields, about 6×6 cm in size and 5 mm apart, were drawn on a plaster mask of the upper part of the cranium and the centres of these four fields were marked. The position of the tumour was indicated in the roentgenogram of the phantom and its position in the plaster mask was then marked on a metal rod introduced at right angles to the sagittal plane. The points of entry and exit of the central ray through the plaster mask in each of the four fields were obtained by introducing a rod through the centre of each field (entrance of central ray) and the centre of the tumour until the tip of the rod met the mask. The points of entry and exit as well as the fields were then transferred to the skull phantom.

The measurements were made with microcondenser chambers of the Sievert's type, modified according to LIDÉN-SKÖLDBORN. The chambers were read with a specially adapted Philips dosemeter. Calibration was performed with the chambers placed 16 mm above a Mix D phantom against a Baldwin-Farmer X-ray substandard chamber, which also has a relatively small measuring volume. As far as measurements inside the phantom are concerned, the directional sensitivity of the cham-

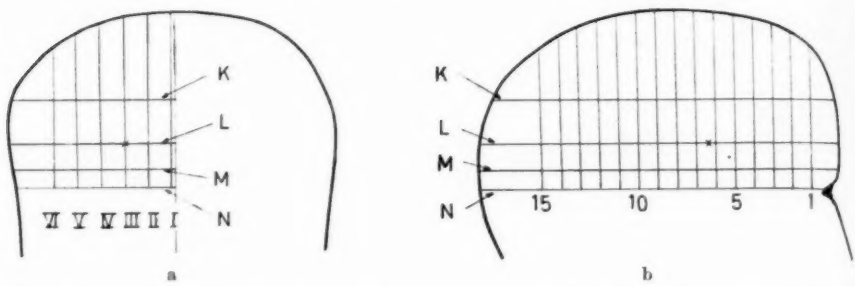

Fig. 3. Schematic illustration of the geometric measuring system. a) Position of the 6 sagittal planes and of measuring planes. Sagittal plane I lies 2.5 mm to the right of the middle of the skull. b) Positions of holes (1 to 15) in plane I, spaced 10 mm apart. The imaginary tumour is spherical and 3 cm in diameter. Cross indicates centre of tumour: III 6.4, L.

bers is negligible so that they can be used in any position in relation to the direction of the rays. All chambers have the same energy dependence which varies on the average by 5 per cent in the HVL region of 0.09 mm Cu (100 kV) to 1.6 mm Cu (170 kV). The sensitive volume of the chambers is 0.03 cm^3, *i. e.* so small that the measurements may be regarded as point measurements with the measuring point 4 mm below the top of the chamber.

The head phantom was fixed in a special frame and the direction of the rays was adjusted by means of a back pointer. The field of treatment was limited with a lead mask 2 mm thick and large enough to prevent simultaneous irradiation of any other part of the phantom. To control the stability of the roentgen tube a monitor chamber was mounted in the beam but in such a way that it did not produce a shadow in the irradiated field.

Measurements were made in four horizontal planes (Fig. 3) perpendicular to the drilled holes. The distance between the planes was 20, 12, and 8 mm, from above downwards; they will be referred to as K, L, M and N. The L-plane passed through the centre of the imaginary tumour. As to the upper two fields (3 and 4), measurements were also made at different points as close to the bone as possible and the contribution by each of the four fields was studied. The chambers were placed in a horizontal plane and at a perpendicular distance of at least 2 cm from the adjacent chambers; in order to have the chambers in the same plane the floors of the holes were corrected so that their vertical co-ordinates differed by an integral number of half centimetres. Two measurements, on an average, were made per measuring point. The surface dose was meas-

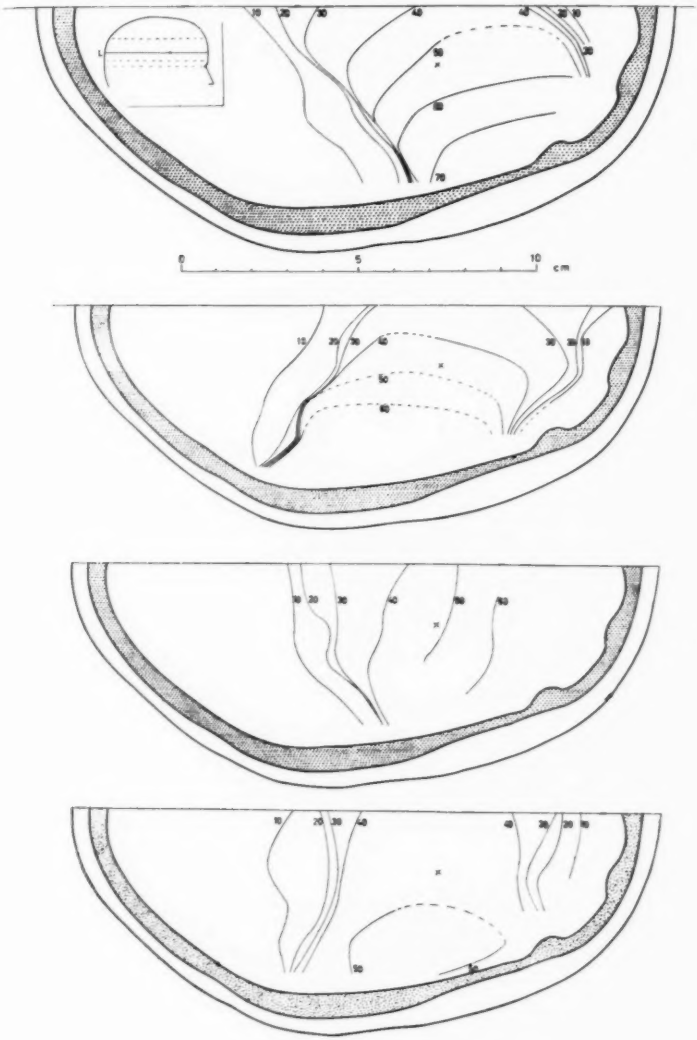

Fig. 4. Shapes of isodose curves in L-plane on irradiation, from fields 1 to 4, respectively. The calotte, outer lining of Mix D, and centre of tumour are indicated. The difference between the isodose curves is 10 %. Uninterrupted lines denote courses determined by measurements, interrupted lines the probable course between remote measuring points. The small diagram, inserted to the left in field 1, indicates the measuring plane.

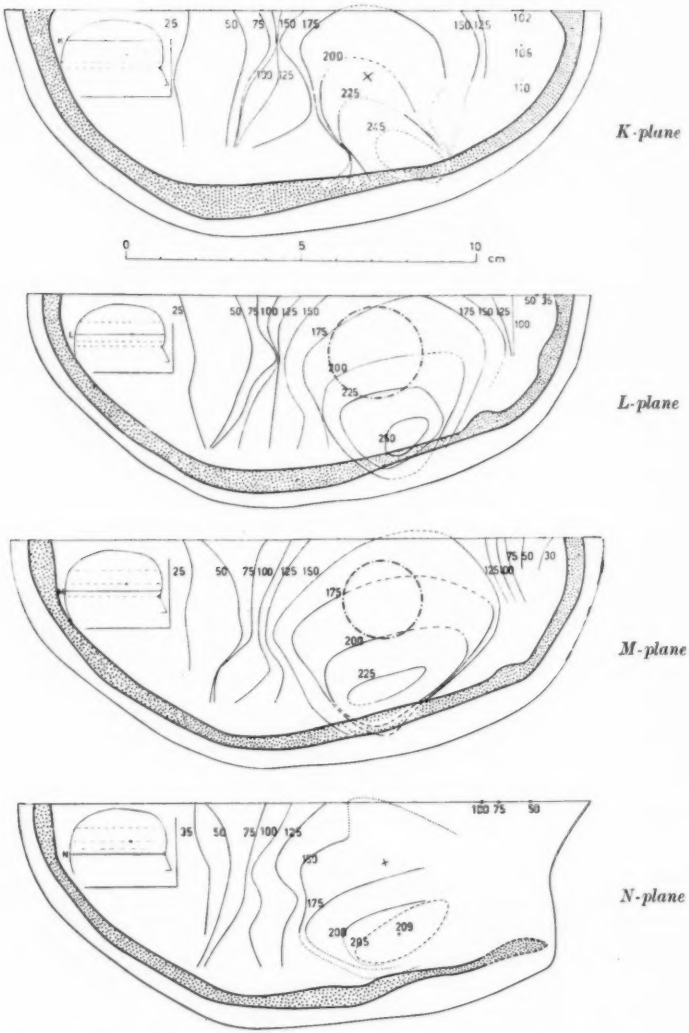

Fig. 5. Isodose diagrams of total dose from all 4 fields in measuring planes. Extent of the tumour in L- and M-planes is outlined. The tumour does not reach the K- nor N-planes; the projection of its centre in these planes is indicated by a cross. The difference between the isodose curves is as a rule 25 %. Uninterrupted isodose curves indicate the courses determined by measurements, dotted lines indicate interpolated values. Interrupted lines denote probable course of isodose curves between remote measuring points.

Small diagrams, inserted to the left indicate the 4 measuring planes.

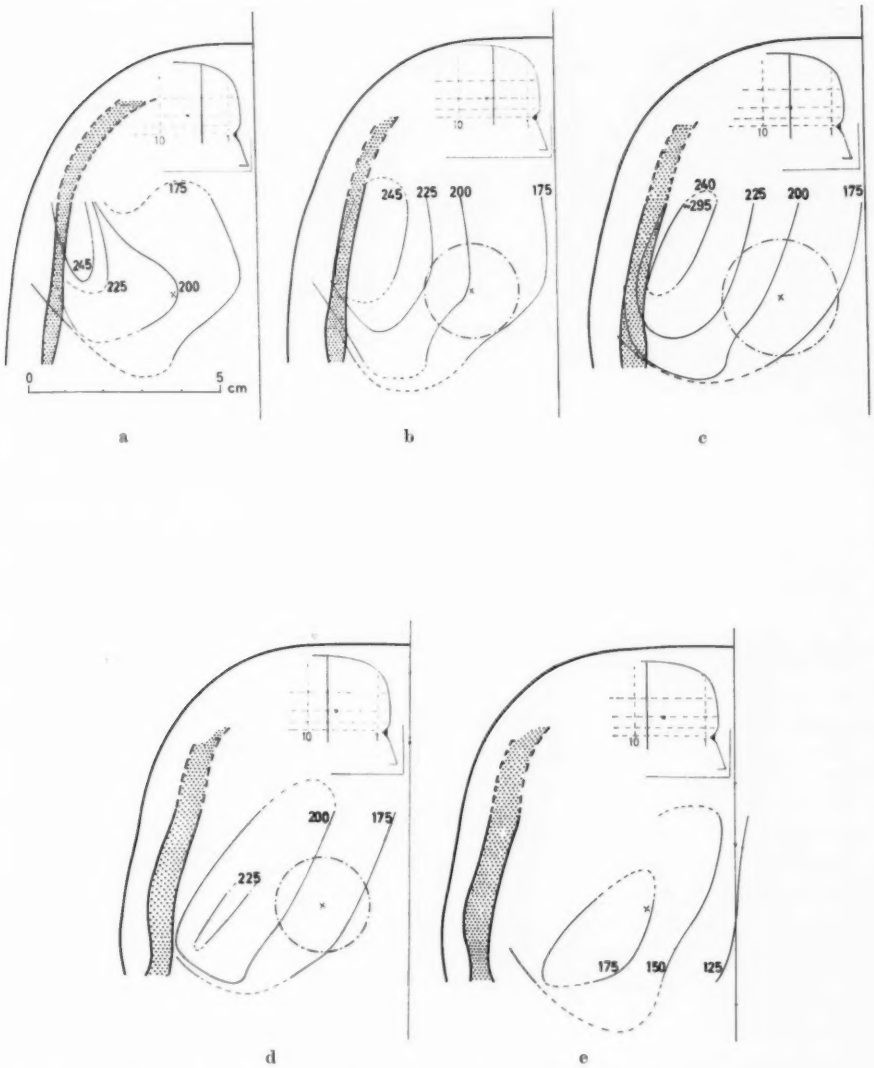

Fig. 6. Frontal sections, perpendicular to sagittal plane, through tumour and immediate surroundings: a) and b) 2 cm and 1 cm, respectively, in front of tumour centre; c) through tumour centre; d) and e) 1 cm and 2 cm, respectively, behind tumour centre. Extent of tumour is outlined in b) to d). The projection of the centre of the tumour is marked in each section.

ured with 2 micro-chambers placed in the middle of the field perpendicular to the direction of the central beam and with the sensitive ends towards each other. The focus—skin distance was 50 cm throughout and the radiation quality 170 kV with a filter of 0.5 mm Cu + 1 mm Al giving a HVL in Cu of 1 mm. It should be pointed out that this quality of radiation holds only for the radiation in air and that the quality of the radiation on the skin and at a depth of 8 cm, for example, corresponds, according to GREENING-WILSON (1951), to a HVL in Cu of approximately 0.8 mm and 0.7 mm, respectively.

The effect of scattered radiation from the thorax on the depth dose in the skull was studied by measurements at 6 points in the skull with and without the thoracic phantom in position. The thorax and the shoulder girdle were built up of a human skeleton with Mix D as a substitute for the soft tissues. The contribution proved to be negligible and to lie within the errors of measurement.

B. Results of measurements

The roentgen dose at the measuring points was determined after irradiation of each of the four fields separately. By means of these measured values, diagrams for the intersection lines of the four measuring planes with the sagittal planes I—VI were constructed. These diagrams showed the variation in the depth dose along the intersections. The isodose curves in each of the four measuring planes were then constructed with the aid of the diagrams. Such isodose curves are exemplified for the L-plane (Fig. 4) were the dose contribution from each field to the total depth dose can be studied.

The anterior border of *field 3* could not be measured for anatomical reasons. The distribution of the dose in the tumour region is more uniform in the L-plane in *fields 3* and *4* because of the longer distance traversed by the radiation before it reaches the L-plane.

By the addition of the depth doses from all four fields at the points measured, we obtain, as in the diagrams mentioned above, the different values for the total percentage depth doses for each intersection of the sagittal planes with the respective measuring plane. It was assumed that an equal surface dose was delivered to each of the four fields. The isodose curves in the four measuring planes of the total percentage depth dose were then constructed as before (Fig. 5). The position of each measuring plane relative to the imaginary tumour region, which has a diameter of 3 cm, is indicated in the diagram. The K-plane lies above the tumour, the L-plane runs through its centre, and the M-plane passes through its lower half; the N-plane is situated just below the tumour.

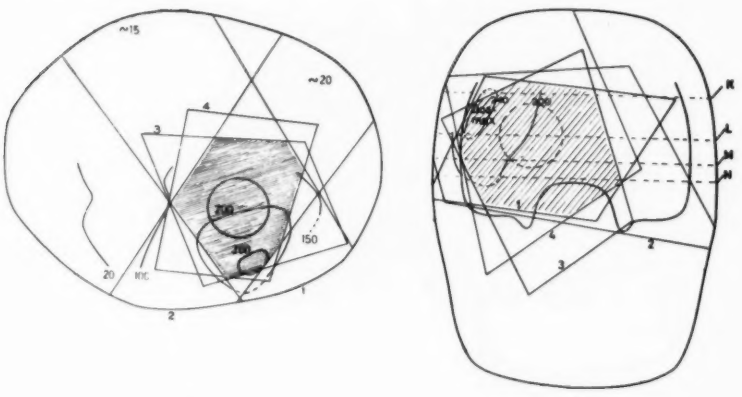

Fig. 7. a) Intersection of beams with L-plane in both hemispheres. Hatched region is irradiated from all fields. Some added percentage depth doses from all 4 fields inserted. b) Intersection of beam with frontal section through centre of tumour.

The intersection of the four beams with the L-plane (Fig. 7 a) and with a frontal section through the centre of the tumour (Fig. 7 b) are marked in both hemispheres, and certain isodose curves and measured values, as well as the outline of the tumour, are given. This permits assessment of the size of the brain volume irradiated and of the size of the region which receives the largest doses. In Fig. 7a the isodose curve for 250 per cent is far out in the lateral margin within the region where the adjacent corners of all four fields meet and thereby contribute to the build-up of the doses. The shape of the isodose curve for 200 per cent and 150 per cent shows a distinct dependence on the contribution of the dose from the various fields. The 100 per cent curve describes a bend, the cause for which may at first not be clear. This could, however, afterwards be well explained by the fact that all four fields crossed just in this region. In the posterior part of the brain the 20 per cent curve illustrates the low doses in the regions lying outside the beams; furthermore, the dose at the periphery of the beams in the opposite half of the brain is only a fraction of that applied in the tumour region and its surroundings. Fig. 7b shows the region of the absolute dose maximum for the entire irradiated volume.

It should be observed that Fig. 7 represents only one section through the brain. The course of the isodose curves is quite different outside these sections. This is obvious from a number of frontal sections before, through, and behind the centre of the tumour (Fig. 6). Figs. 5 and 6 represent the three-dimensional dose distribution inside and outside the irradiated portion of the brain. The absolute maximum dose indicated in Fig. 6 lies in none of the measuring planes, but just below the K-plane.

C. Discussion of the results of the measurements

The course of the added isodose curves illustrates the distribution of the dose within the examined half of the skull by the multi-field technique employed. The purpose of this technique is to secure a high tumour dose. It is obvious that massive irradiation is limited to the tumour region, and its immediate neighbourhood, while the posterior half of the brain and the anterior portion receive only small amounts of radiation. The dose maxima measured (Figs. 5 and 6) were, however, in all planes located outside the tumour region and dose differences of 25 per cent and more between the tumour centre and respective dose maximum can be read. The maximum dose in the deepest measuring plane (N) was 1 to 2 cm below the surface of the brain. In the M-plane it lay quite close to the surface of the brain, while the maximum in the upper two measuring planes (L and K) was situated both on the brain surface and in the calotte and soft tissues outside. The largest doses were measured in the two upper planes. It was also clear that the distribution of the dose in the region of the tumour and its immediate neighbourhood was uneven. The tumour received a much larger dose in its upper half and in addition the decrease of the percentage depth dose from the calotte to the sagittal plane was large. The dose maxima in the different planes were on the average 20 per cent larger than the dose in the centre of the tumour, with peak values of up to 50 per cent. The dose in the upper lateral part of the tumour region was about 25 per cent larger than in the lower medial portion. The percentage difference between the dose in the tumour region irradiated least, and the dose in the absolute maximum (Fig. 6c) was about 70 per cent.

The irregularity of the distribution of the dose in the region of the tumour is due to the position of the fields. The region around the absolute dose maximum represents a hot-spot with considerable risks of overdosage in this section, while the possibility of underdosage in the lower medial parts of the tumour is appreciable. An example of such overdosage is demonstrated in a vertical section through a brain irradiated by a similar technique. A well-defined necrotic region was seen near the surface of the brain with tumour-rests in the periphery, especially in the deep tissues (Fig. 8). In this case the fields were placed higher up on the calotte.

It should be pointed out in this connection that for biological and physical reasons the amount of the dose absorbed in the calotte expressed in rad units (1 rad = 100 erg/g) is much greater in all measuring planes than those given above in roentgen units. The risk of radiation damage to the calotte is therefore obvious.

In order to determine to what extent the observed values agreed with theory, the depth dose ratio at different measuring points was arrived at

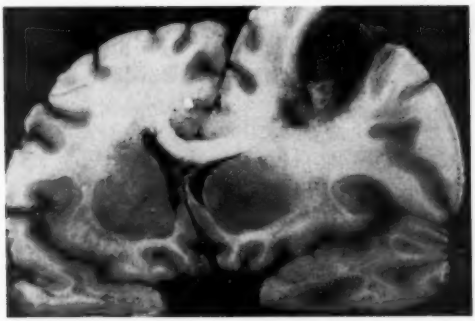

Fig. 8. Vertical section through necrosis in hot-spot region of brain irradiated by the method.

by calculating separately the amounts of the contribution of primary radiation and secondary radiation at these points. The influence of the skull bone was taken into account in the former calculation but not in the latter. The primary dose was calculated in the ordinary way assuming exponential absorption. The absorption coefficient for bone was obtained from SPIERS' (1946) tables. The contribution from the secondary radiation was worked out according to MEREDITH-NEARY (1944), using the values of HORSLEY and ASPIN (1956). The calculation of both the primary and the secondary radiation doses refers therefore only to the 'Central Axis Depth Dose Data' (1953). In order to obtain those plane surfaces which are needed to permit application of this method of calculation, the field studied was divided into two halves, each of which was then approximately plane. A co-ordinate system was introduced employing the set of drilled holes in relation to which all necessary points were measured, this permitting an exact geometrical calculation.

The theoretical calculations for two points showed good agreement with the measuring results.

From the experimental measurements the following conclusions may be drawn.

With the method of treatment used, a maximal dose is delivered outside the tumour region near the surface of the brain.

The absolute dose maximum is much greater than the dose received at the centre of the tumour. The distribution of the dose in the region of the tumour is uneven.

The measured depth doses agreed well with the theoretical values calculated for a few points according to MEREDITH-NEARY's method.

II. Investigation of the possibilities of improving the intracranial distribution of the dose

The method of treatment described may, as shown previously, produce complications due mainly to the development of undesirable positions of the hot-spot regions and consequent necroses of the brain tissue. Various alternatives for improvement of the dose distribution by this technique without any appreciable difference in the tumour or integral doses were therefore investigated.

Variation ni field doses

With the technique employed (Fig. 2) the beams delivered to the various fields cross one another just below the surface. Since the total depth dose consists of the contributions from these fields only and since the intensity from each field decreases with the depth, the total dose must also decrease with depth. Relative changes in the size of the skin dose delivered to the various fields cannot therefore prevent the absolute dose maximum from being delivered just below the surface. Certain improvements, however, could be envisaged.

In the alternative measured (Fig. 7), which in the following is called *alt. E* and in which the skin dose was equal for all four fields, the maximum region in the L-plane extending through the centre of the tumour (Fig. 3), was localised outside the tumour in the region V-5 to V-6 and VI-5 to VI-6 (Table 1). A shift of the maximal region in the L-plane to III-6 and III-7, and to II-6 and II-7, *i. e.* the region of the middle of the tumour, is desirable (Table 1).

As in clinical practice, the skin dose per field in the experimental examination was chosen at 4,000 r. It is believed that this dose can be increased to 5,000 r. In order to shift the maximum region, *field 1* should

Table 1

Percentage depth doses measured in the L-plane in the tumour region (T) and in the region of the maximal dose (S)

Localization	*Field 1*		*Field 2*		*Field 3*		*Field 4*		Total	
T { II-6 and II-7 ..	50.4	48.0	39.2	40.6	49.0	44.8	44.8	46.4	183.4	179.8
T { III-6 and III-7 ..	53.8	50.8	45.0	48.8	50.8	45.0	48.6	48.0	198.2	192.6
S { V-5 and V-6	73.2	70.4	61.0	62.0	62.8	54.4	53.4	54.2	250.4	241.0
S { VI-5[1] and VI-6 ..		78.0		71.0		52.0		49.6		250.6

[1] Not measured.

Table 2

Alternatives (I and II) for modifying the distribution of the skin dose
Maximal dose per field 5,000 r

	I	II
Field 1	3,000 r	3,000 r
Field 2	4,000 r	3,000 r
Field 3	4,000 r	5,000 r
Field 4	5,000 r	5,000 r

receive a lower dose (Table 1); it not only gives the largest contribution to the maximal dose but a high tumour dose. The dose in the maximum region is also large in *field 2*, and *field 3*, in particular, should receive a larger skin dose. *Field 4* is most favourable for reducing the maximal dose and also gives a fairly high contribution to the tumour region. On the basis of these considerations certain alternatives for the distribution of the skin dose were selected (Table 2). The decrease in the skin dose to *fields 1* and *2* was limited to 1,000 r in order not to reduce the tumour dose too much, and at the same time the integral dose was retained almost unchanged.

In the calculation of these alternatives only small differences were found compared with the original values (Table 3); the added depth dose in the maximal region of the L-plane at a given point was decreased by 2 % in alternative I and in alternative II by a little more than 4 %. The doses received by the tumour region were almost the same.

Change in shape and position of the fields

Irradiation of the entire tumour via each field with a given total size of field and given skin dose would broadly speaking imply a maximum tumour dose; any change in the positions of the field would only increase, or at any rate not decrease, the distance between the centres of the tumour and the field.

The maximum dose, however, would at the same time come to lie near the surface of the brain in healthy tissue. The size and site of the dose maximum might be favourably modified by adjusting the site and shape of the fields. This possibility is discussed, it being understood that the total skin surface irradiated and the total skin dose (4,000 r) applied to each field remain unchanged. The methods would then be comparable.

Modifications of the method to avoid the beams crossing one another too close to the surface might consist of the following measures.

Table 3

Modification of size of maximal dose in the K- and L-planes by adjustment of the skin dose
The tumour is situated in sagittal planes II and III
The region of the maximal dose is situated in sagittal planes V and VI

	Original alternative			Alternative I			Alternative II		
	5	6	7	5	6	7	5	6	7
K-plane									
II		185	180		180	180		185	180
III		200	195		200	190		200	190
IV									
V		245	175		250	190		255	180
VI	295[1]	—	—	295[1]	—	—	295[1]	—	—
L-plane									
II		185	180		180	180		185	180
III		200	195		200	190		200	190
IV									
V	250	240	230	245	235	230	245	235	225
VI	—[2]	250	225	—[2]	245	220	—[2]	240	220

[1] The depth doses given for VI-5 in the K-plane are calculated.
[2] Not measured.

1. Centering the beams beyond the centre of the tumour;
2. Decreasing the number of fields with a corresponding increase in the size of the remaining fields, or increasing the number of fields and decreasing the size of each;
3. Placing the fields wider apart;
4. Changing the shape of the fields.

1. *Centering of the beams beyond the centre of the tumour.* This modification would imply that the beams would converge deeper in the tissues (Fig. 9). It was rejected, however, as it would increase the margin on one side of the tumour but decrease it on the other. Since the increased margin is only of significance for secondary radiation to the tumour the maximum could be moved inwards by making the fields smaller.

2. *Decrease in the number of fields with corresponding increase in the size of the remaining fields or increase in the number of fields with a corresponding decrease in their size.* Any decrease in the number of fields below 4 with simultaneous increase in field size would probably be disadvantageous. It is true that the tumours receive a larger amount of secondary radiation through large parts of the fields lying outside the tumour area but these parts could be used better by collecting them to a new field directed against the tumour (JOHNS 1953).

The number of fields might theoretically be increased by dividing the irradiated skin surface, for example, into 6 smaller fields. This technique involves two regions where the corners of four fields meet. The dose received under the surface of these regions could possibly be made smaller than that received by the tumour because two new fields contribute to the tumour dose but only to one of the above-mentioned regions. In this way a better ratio would be obtained between the tumour dose and the maximal dose outside the tumour and at the same time the dose maximum would be moved further in. Any division of the skin surface into more than 4 fields, however, involves considerable risk of the margin around the tumour being too small; for this reason this alternative was not investigated further.

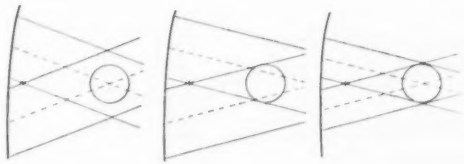

Fig. 9. Focusing beyond tumour results in intersection of beams at deeper level. The same effect is obtained with smaller fields.

3. *Separation of the fields.* Since the depth dose for a given radiation quality decreases rapidly with the depth, the fields should be placed in the region closest to the centre of the tumour; in this way the change in the tumour is kept within narrow limits. *Field 1* (Fig. 10 a) should therefore remain in its present position, as anterior as possible, to provide room for *field 2* whose depth dose contribution decreases rapidly if it is moved backwards. Any forward shift of *field 1* will influence its optimal position in relation to the tumour only slightly. Separation of the three fields around *field 1* produces the following possibilities. If *field 2*, for example, be displaced 7 cm along the line of the intersection of the skull with the L-plane, the distance from the centre of the field to the centre of the tumour will be increased from 55 mm to 95 mm (Fig. 10a). A corresponding movement of the centre of *field 4* (Fig. 10b) 7 cm along the periphery of the skull parallel to the sagittal plane will increase the distance between the field and tumour centres from 75 mm to 100 mm. If the large tumour dose is to be retained, *field 2* should thus be moved only a short distance, while the movement of *field 4* may be greater. *Field 2* may be moved backwards, and possibly downwards or upwards; an upward movement of this field, however, implies that both *field 2* and *field 4* will have longer skin—tumour distances. If *field 4* is moved over as far as the other side of the cranium, the distance between the tumour and field centres will be about the same as on moderate displacement backwards. *Field 3* can be

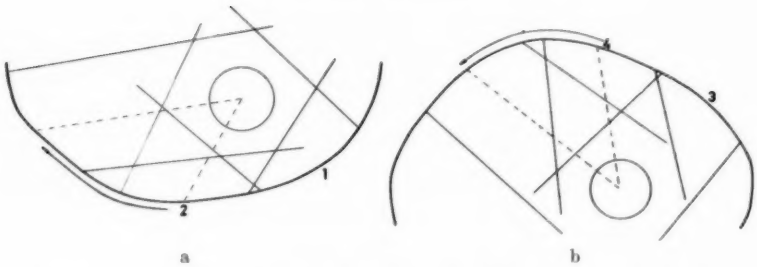

Fig. 10. Diagrams of position of fields and possible modifications in relation to tumour. a) Horizontal section through tumour centre and (b) vertical.

moved forwards towards the forehead with advantage; one of its corners is thereby moved from the critical region and (Fig. 10 b) the distance between the field and tumour centres is hardly changed. If this field is moved towards the other side, the distance to the centre of the tumour increases with a consequential decreasing tumour dose; its contribution to the dose maximum is likewise decreased. *Field 3* should thus be moved forwards, possibly somewhat over the midline.

As shown in Fig. 11, the position of *field 1* should not be altered; *field 2* should be moved backwards, *field 3*, forwards as far as possible, perhaps even over the midline, and *field 4* backwards or over to the other side of the skull. The approximate positions of the fields in Fig. 11 a are referred to below as *alt. F*. When *field 4* is placed on the opposite side of the skull, the positions of the fields are referred to as *alt. H* (Fig. 11b).

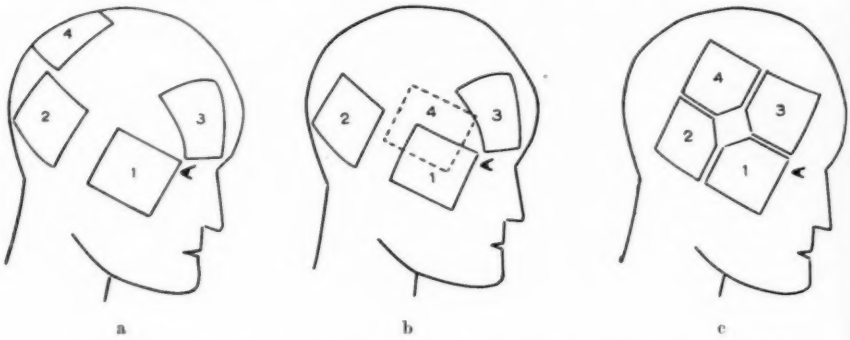

Fig. 11. Diagrams of distribution of fields according to: a) *alt. F*, b) *alt. H*, and c) *alt. G*.

4. *Change in the shape of the fields.* Any change in the shape of the fields must, of course, influence the region with the four adjacent corners. Elimination of these corners, *alt. G* (Fig. 11c) moves the dose maximum inwards and even decreases its size. Since the margin to the tumour is largest at the corners, such a limitation of the field is possible (Fig. 12). The amount cut off should be in proportion to the extent of the tumour and the necessary margin of tissue irradiated around the tumour, *i. e.* 'b' should not be less than 'a'. Other possible sections of these corners offer only insignificant deviations. The use of circular fields (cutting off of all four corners of each field) produces roughly the same change in the dose maximum as elimination of four adjacent corners, but gives a somewhat smaller tumour dose.

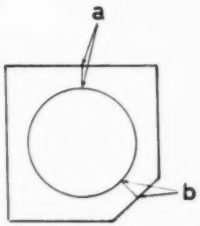

Fig. 12.

The effectivity of the changes in the fields described above will now be evaluated by comparison with the distribution of the fields used in the experimental investigation, *alt. E.* (Fig. 2.)

In order to assess the position and size of the maximal dose and the size of the tumour dose as compared with the original without measurements — which would be time-consuming — the geometry of the beams must be known. This is necessary in order to determine the position of an imaginary point in relation to a given beam for which the dose is calculated and for the estimation of the position of the maximal dose inside the skull. In comparing the various alternatives with the measured alternative, it is necessary to use the dose maximum in the measuring planes, the absolute dose maximum being localized somewhere between the K- and L-planes.

On projection of the fields in the selected horizontal plane the corners of the projections are connected by straight lines, the curve of the fields of the skull being thus ignored. The region irradiated directly from all four fields is shown hatched in Fig. 13. It is possible approximately to judge from the projections where the maximum is situated in the selected plane. Determination of the position of the maximum points in this way is not possible in all cases but may be performed with a good approximation in the three alternatives studied. It is exemplified for *alt. F* in the L-plane in Fig. 13.

The size of the dose at a calculated point was obtained according to the following scheme. The length in the material of the impinging ray, *i. e.* the ray between the focus and the point selected was calculated. For a corresponding depth and corresponding effective field surface A ($A = B \cos \alpha$ where A lies at right angles to the central beam, B is the plane surface which approximates the true curved surface and α represents the angle between A and B) the 'Central Axis Depth Dose Data', Section 3,

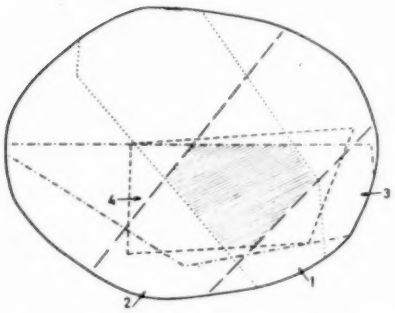

Fig. 13. Horizontal section showing intersection of beams in L-plane according to *alt. F*. Cross indicates tumour centre.

give a certain value which corresponds to the percentage depth dose at the points on the central beam in a plane surface *A* (Fig. 14). The approximation thus consists in ignoring the positive or negative contributions of secondary radiation from the hatched volumes in Fig. 14. When point P is deep, these two are small compared with the other secondary radiation; if the depth is small the primary contribution is predominant.

Since the dose at a certain point in the central ray is greater than elsewhere in the beam in the same plane, correction for this had to be made. The distance to the nearest limiting surface of the beam was calculated and the difference between the dose in the central ray and the outer ray at the same depth was read from isodose curves. In certain cases, in which the imaginary point was judged to be lying at the corner of the field, a further improved approximation was obtained by calculating, according to MEREDITH-NEARY's method, the difference between the dose received at the corner and at the centre of the field size under discussion. Bone absorption was taken into account by multiplying the results by 0.94 to 0.97, factors obtained from personal measurements.

Application of this method to the original distribution of the fields gave good agreement with the measurements made.

The results of the comparison of the various alternatives just discussed are given in Table 4.

Calculations were made for alternatives F, G and H (Fig. 11) and compared with the experimental values (*E*) for the original distribution of the field (Fig. 2). The maximal dose is given for both the K- and L-planes where it was possible to compare the values with the original alternative. The centre of the tumour is located in the L-plane. The material is presented in Table 4, in which the values refer to a 100 per cent skin dose.

Alt. G, i. e. elimination of the adjacent corners of the four fields, may be regarded as superior to the original alternative as regards

the position and size of the maximal dose; the skin dose and the dose at the centre of the tumour are unchanged. *Alt. F*, with separation of the fields, with *field 4* far back (Fig. 11a) gives smaller maximal doses but at the same time 13 per cent lower tumour doses. With a skin dose of 4,000 r per field the centre of the tumour receives 6,800 r, as against an original 7,800 r. This also applies to *alt. H*. The tumour dose decreases in this case to 6,700 r. But since the dose in the maximal region decreases rapidly from 11,800 r to 8,300 r and 7,700 r, respectively, these alternatives, especially *alt. H*, may be considered as considerable improvements on the original technique. In *alt. H* one might also expect a more even distribution of the dose in the entire tumour than by the other alternatives. This was verified by calculations for a point in the most medial part of the tumour.

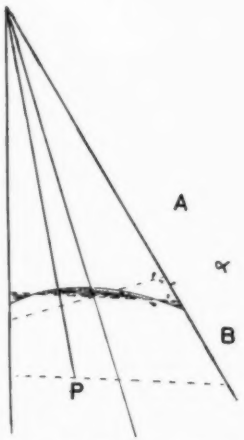

Fig. 14. Diagram illustrating approximate calculation of depth dose.

Change in radiation quality and focus—skin distance

The next step was to investigate the influence of a change in the radiation quality and the focus—skin distance. For this purpose the percentage depth-dose values ('Central Axis Depth Dose Data') were used for 1 mm Cu HVL and FSD 50 cm, 2 mm Cu HVL and FSD 60 cm, and 5 mm Cu HVL and FSD 100 cm, which is the upper limit of the HVL and FSD in the 200 to 400 kV region given in the tables.

Under the last mentioned conditions (5 mm Cu HVL) conversion of the experimental values for the original distribution of the fields *alt. E.* shows that the ratio between the skin and tumour doses decreases by about 16 %, *i. e.* an improvement, while the increase in the ratio between the tumour dose and the maximal dose in the L-plane will show an improvement of about 9 %. From this point of view the improvement is thus relatively moderate. There is a strong indication, however, for the use of radiation with a larger half-value layer than 1 mm Cu. The energy absorption in the calotte is decreased considerably (*e. g.* Balz, Birkner and Wachsmann 1955) and since the hot-spot region lies partly in bone, this is of importance. At a depth of 1 cm the absorption of energy in bone is 1.5 times greater for the quality 1 mm Cu HVL than for 2 mm Cu HVL (Spiers 1949). The biologic effect is closely related to the absorption of energy.

Table 4

Results after change in position of the fields

Alt.	K-plane			L-plane			Dose in centre of tumour %	Skin dose per field %
	Max. dose site		Max. dose %	Max. dose site		Max. dose %		
	x	y		x	y			
E	*VI-0*[1]	5.5	295	*VI-0*	6.0	250	195	100
F	*IV-8*	5.6	205	*V-0*	6.0	205	170	100
G	*V-0*	5.8	255[2]	*V-2*	5.7	230	195	100
H	*IV-8*	5.6	195	*V-5*	6.4	200	165	100

The x-coordinate indicates the position in relation to the medial plane; the y-coordinate the position in the fronto-occipital direction (Fig. 3).

[1] Index denotes distances in mm from sagittal planes.
[2] For a plane 3 mm below the K-plane. Only beams from 3 fields intersect in the K-plane. The beam from the fourth field passes a few mm below the K-plane.

The use of harder radiation somewhat reduces the risk of underdosage of the deeper parts of the tumour and secures a more even distribution of the dose in the region of the tumour.

Discussion

The possibility of decreasing the dose in the hot-spot region and moving it nearer the tumour region without any appreciable change in the tumour or integral doses was investigated. In the alternatives discussed the maximal dose, *i. e.* the hot-spot region, is situated laterally between the K- and the L-planes.

A change in the dose delivered via each field was found to have only a slight influence on the dose in the hot-spot region. A maximal decrease of this dose by 4 % was calculated for the K- and L-planes (Table 3) but the dose in the tumour region was unchanged.

On change in the shape and position of the fields it was found for the L-plane (Table 4) that elimination of the adjacent corners of the four fields *alt. G* produced a decrease of 8 % in the maximal dose as compared with the original alternative and a slight shift of the maximal dose towards the centre of the tumour. As to *alt. F* and *alt. H*, they gave a considerable decrease, *i. e.* improvement in the size of the maximal dose, namely 18 % and 20 % respectively, and a medial shift of its position by 0.5 to 1 cm. The tumour dose was, however, somewhat decreased, *i. e.* impaired. The corresponding percentual values in the K-plane are as follows: 13 % for *alt. G* and 30 % and 34 % for *alt. F* and *alt. H*, respectively. The total

Table 5

Comparison of the various alternatives with reference to results of measurement in the K- and L-planes

Skin doses according to alternative II (table 2)

Alt.	2 mm Cu HVL 60 cm FSD			5 mm Cu HVL 100 cm FSD		
	Change in ratio tumour dose/max. dose		Change in tumour dose %	Change in ratio tumour dose/max. dose		Change in tumour dose %
	K-plane	% L-plane		K-plane	% L-plane	
F	24	10	—11	32	15	+ 2
G	23	12	+ 8	31	15	+20
H	37	16	— 9	44	21	+ 4

hot-spot region, therefore, shows a medial displacement in position and at the same time the tumour dose is decreased.

Within the range of variation given, the position of the maximal dose in the L-plane is influenced only slightly by a change in the radiation quality and focus—skin distance; at the same time the ratio between the tumour dose and the maximal dose is decreased by 9 % with a simultaneous increase in both doses. The greatest advantage is the reduction in the energy absorption in bone. As to the K-plane, the changes are smaller.

A combination of all of the above-mentioned possibilities was studied with special reference to the distribution of the dose in the L-plane which passes through the centre of the tumour (Table 5). This showed that *alt. F* gave a total improvement (15 %) of the ratio between the dose in the centre of the tumour and the maximal dose, *alt. G* producing a similar improvement of 15 %, *alt. H* 21 %, and that the tumour dose was improved by 2 %, 20 %, and 4% respectively. All these improvements should obviously be achievable. The corresponding values for the K-plane would be 32 %, 31 % and 44 %. With our apparatus which permits the use of a radiation quality corresponding to a HVL of 2 mm Cu and a FSD of 60 cm the corresponding improvements in the ratio between the dose in the centre of the tumour and the maximal dose *F*, *G*, and *H*, would be 10%, 12 % and 16 % for the L-plane and 24 %, 23 % and 37 % for the K-plane respectively; the tumour dose would, however, thereby be changed, namely by —11 %, +8 %, and —9 %, respectively. Under the conditions described (certain total size of fields, certain skin dose, and high tumour dose) the investigation showed that improvements in the distribution of the dose, measured experimentally, in the alternative can be achieved by eliminating the four adjacent corners. If a reduction in the tumour

dose can be accepted, both *alt. F* and *alt. H* also produce a considerable improvement in the ratio between the tumour and maximal doses.

The hardness of the radiation should exceed a HVL of 1 mm Cu in order to diminish the risk of radionecrosis in the calotte.

Only by a radical modification of the technique, *e. g.* the use of MeV radiation, or the employment of a moving field technique, possibly in combination with the former, can any sweeping improvement be expected.

Acknowledgements

I wish to thank A. Alm, M. A., of the Department of Radiation Physics, for his kind help with the mathematical calculations.

SUMMARY

Investigations of the distribution of the dose by a technique with 4 adjacent fields for irradiation of cerebral tumours were carried out on a skull phantom, the measurements being made with ionisation chambers. The results showed that the maximal dose was delivered outside the centre of the tumour near the surface of the cerebrum and that it was much larger than the dose received at the centre of the tumour, and that the distribution of the dose in the region of the tumour was uneven. The risks of this distribution of the dose, as well as those of underdosage and overdosage, are discussed. Various possibilities of improvement were investigated and included variation in the dose delivered via each field, variation in the shape and position of the fields, and changes in the radiation quality and the focus—skin distance.

ZUSAMMENFASSUNG

Untersuchungen über die Dosisverteilung bei einer Behandlungstechnik mit vier eng beieinander liegenden Feldern zur Bestrahlung von Hemisphärtumoren sind an einem Schädelphantom mit Hilfe von Ionisationskammermessungen durchgeführt worden. Die Ergebnisse zeigen, dass die Maximaldosis ausserhalb des Tumorzentrums in der Nähe der Hirnoberfläche gelegen ist, dass sie bedeutend grösser als die Dosis im Tumorzentrum ist und dass die Dosisverteilung innerhalb des Tumors ungleichmässig ist. Die Gefahren einer derartigen Dosisverteilung für Überdosierungskomplikationen und für Unterdosierung werden diskutiert. Verschiedene Verbesserungsmöglichkeiten sind untersucht worden, nämlich die Variation der Feldbelastung, Veränderungen der Lage und Form der Behandlungsfelder sowie Änderungen der Strahlenqualität und des Fokus—Hautabstandes.

RÉSUMÉ

L'auteur a étudié sur un fantôme de crâne la distribution des doses obtenue avec une technique à quatre champs adjacents pour l'irradiation de tumeurs cérébrales; les mesures ont été faites avec des chambres d'ionisation. Les résultats montrent que la dose maximale est distribuée en dehors du centre de la tumeur, près de la surface du cerveau, qu'elle est beaucoup plus forte que la dose reçue au centre de la tumeur et que la distribution de doses dans la région de la tumeur est irrégulière. Il étudie les dangers de cette distribution de doses, dangers de sous-dosage et de sur-dosage. Il a examiné différentes possibilités d'amélioration, entre autres en modifiant la dose administrée par chaque champ, la forme et la position des champs, la qualité du rayonnement et de la distance focus—peau.

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A METHOD OF MEASURING THE MASS OF THE THYROID GLAND IN VIVO

by

L. Burkinshaw

Among the physical measurements required in the determination of the mean radiation dose to the thyroid gland in treatment with I^{131}, the least accurate at the present time is that of thyroid mass. Since the accuracy of the dosimetry depends directly upon the accuracy with which this mass is known, it is important that the measurement be made more precise.

The mass is most commonly estimated by palpation, and published series of such estimates (SOLEY et coll. and WILLIAMS et coll.) include errors up to about $\pm$ 40 %, with about one quarter of the observations within $\pm$ 10 % of the true value. However, as will be shown, the errors may be much greater than this.

The method of 'Pneumo-thyroid' (FRANCO et coll.) seems to be capable of comparatively high accuracy, its originators finding no error greater than 10 % in an unspecified number of determinations, but it has not yet been widely used.

Using a preliminary tracer dose of I^{131}, the general distribution of the isotope in the neck can be found with a collimated gamma ray counter, and attempts have been made to use this type of map to calculate the gland mass.

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The only one of these attempts to have been reported and discussed in the literature is that of ALLEN and GOODWIN. They plotted the response of a collimated counter moving with its axis horizontal in a vertical plane in front of the neck, parallel to the median plane of the body, and chose one 'isocount curve' as conforming most closely to the projected outline of the thyroid on that plane. Then, assuming that all thyroids are geometrically similar, they deduced the formula

$$M = k.A.h \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (1)$$

in which M is the gland mass, A the area inside the projected outline of height h, and k a constant. Comparing 10 estimates with operation or necropsy specimens, they found the best value for k to be 0.323 with h in cm and A in cm², giving a maximum error of 25.4 % and an average error of 10.6 %. Similar results have been reported using apparatus giving an automatic record of the counter's response (GOODWIN et coll.).

This accuracy appears to be exceptional in view of two later reports. HIMANKA and LARSSON, using the visual outlines of 44 thyroids at post-mortem, found errors up to about 40 %, with an average error of about 20 %. KELLY reports poor agreement when gland masses measured from 15 'gammagrams' using equation (1) were compared with the true masses found at operation or necropsy, and also when the visual outlines were used in 16 cases, but, as LIBBY points out, the agreement is improved if a value of 0.23 is used for k in equation (1). The spread of errors for the gammagram data is now from −24.7 % to + 75.6 %, with an average error of about 20 % and a standard deviation of the ratio of calculated to true mass of 0.292, the visual outlines giving similar results over a smaller range of masses.

The similarity between the spreads of errors reported in these two papers suggests that this is the usual order of accuracy to be expected from the method, which must therefore be improved if accurate dosimetry is to be achieved. This paper describes two methods developed in an attempt to bring about this improvement. The first was unsuccessful, and will be only briefly described, but from it was developed the second method, by which the masses of certain types of goitre can be measured with satisfactory accuracy.

The preliminary method

This was basically an extension of ALLEN and GOODWIN's technique, using isocount maps of the thyroid in two vertical planes at right angles, each at 45° to the median plane of the body. The maps were plotted using a scintillation counter with a 1″ (2.54 cm) cube crystal of thallium activated sodium iodide, the collimator being a cylindrical hole 7 mm in diameter in a lead shield 6 cm thick. The projected outlines of the thyroid were deduced from the maps by comparing them with corresponding maps of model

Table 1

Accuracy of the preliminary method

Method	$\bar{R}$	Maximum errors (%)	Average errors (%)	σ
Counter method	0.935	+ 89 — 62	+ 42 — 39	0.52
Palpation	0.992	+ 121 — 64	+ 77 — 34	0.63

thyroids, superimposed on the accurate outlines of the models. From these outlines, the volume was calculated by approximate integration from the areas of a series of standard horizontal cross-sections, scaled up or down to fit the dimensions of the projected outlines. Thyroid tissue was assumed to have unit density.

The masses of ten thyroids subsequently weighed at thyroidectomy were estimated by this technique, and also by palpation by a number of observers. The mass of each operation specimen was corrected by adding the surgeon's estimate of the mass of thyroid tissue not removed, which in this series ranged from zero to 20 % of the total mass. The results are summarised in Table 1, where $\bar{R}$ is the mean value of the ratio R of estimated to true mass, and σ is the standard deviation of R. The entries under 'average errors' are the arithmetic mean values of positive and negative errors.

The results obtained from the counter measurements are very disappointing compared with the results of other workers quoted above, and are not significantly better than those of the palpation estimations. Examination of the individual estimations indicated that the most serious errors were introduced in the deduction of the thyroid outlines from the isocount maps, and so an attempt was made to improve the precision of the outlining technique.

Present method

The ideal counter for outlining a radioactive region would give a signal only when its crystal was directly exposed to the source. A counter with a simple cylindrical hole collimator is a poor approximation to this ideal, partly because it has a large 'penumbra' region, in which the crystal is only partially exposed to the source, and also because an extended source entering the circular field of the collimator is exposed only gradually to the crystal. A collimator in the form of a narrow slit, scanning the thyroid with its long width a tangent to the boundary at the point of traverse, has a smaller penumbra in the direction of motion, and exposes the source more rapidly to the crystal, so that it should enable the position of the boundary to be located more accurately.

To apply these considerations, the collimator shown in Fig. 1 was constructed. The material is lead, and the dimensions are given in the figure. The cylindrical part fits in a hole in the counter's nosecap, and the long width of the slit was decided by the crystal size, while the external

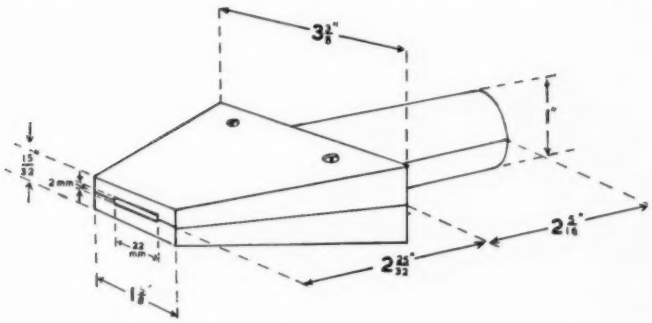

Fig. 1. Schematic drawing of the slit collimator.

shape of the collimator is intended to ensure that the response to a point source moving away from the axis along a line perpendicular to the axis shall fall away without subsidiary maxima.

Used near the edge of the thyroid, this collimator gives only low count rates, so that complete outlining of the gland would take too long to be practicable. It has therefore been used to measure only the major dimensions of the thyroid, *i. e.*, the heights of the lobes and the projected widths of the whole gland on the anterior plane and on two planes at 45° to the median plane, as used in the first method.

The counter is mounted on a gantry-type roentgen-ray tube stand, and in this procedure is arranged to move in a vertical plane. Attached to the counter is a springloaded pencil, which is used to record the position of the counter by making a dot on a vertical sheet of paper. Thus isocount curves can be plotted directly on the vertical paper by making pencil dots whenever the desired count rate is shown on a ratemeter. The patient sits in a chair, fitted with a head clamp, which can be locked in any of three positions, with its back parallel to or at 45° to the plane of motion of the counter.

In this method, the 7 mm diameter cylindrical collimator is first used to draw a single isocount curve, at about 20 % of the maximum count rate, in the anterior projection of the thyroid. This shows the general disposition of the thyroid, and acts as a guide while the slit collimator is used to traverse the length of each lobe with the slit horizontal, and the overall width of the gland with the slit vertical. At the same level as this last measurement, the thyroid is also scanned horizontally in the two 45° projections. As each boundary of the thyroid is crossed, the count rate rises sharply, and it has been customary to note the count rate at about three points on each side of the boundary, again using the pencil to record the position of the counter.

When count rate is plotted against counter position across a dimension of the thyroid, the curve near each boundary can be approximated by two straight lines, intersecting at a point where the crystal is first directly exposed to the radioactive material. Thus the distance between the two intersections is equal to the dimension being measured, plus the effective width of the slit. Phantom experiments showed that it is sufficiently accurate to take the effective width as 3 mm when the tip of the collimator is 7 or 8 cm from the thyroid.

The background of the counter is about 0.5 counts per second, and with a thyroid containing about 0.5 μC of I^{131} per g, the count rate rises to 2 or 3 counts per second, 1 cm inside the boundary. With such low count rates, careful measurement of the five principal dimensions takes $1^1/_2$ to 2 hours.

Calculation of the thyroid mass

Formulae relating the mass of a thyroid to its dimensions were postulated from the following considerations. Let w_R, w_L be the projected widths of the gland on the two oblique lateral planes, and h_O its overall height. Then the thyroid lies inside a volume $w_R w_L h_O$. However, part of this volume is occupied by the cylindrical trachea of radius r, so that the volume available to the thyroid is $w_R w_L h_O - \pi r^2 h_O$. Suppose it is assumed that the thyroid always occupies the same fraction of this volume. Then we find the volume V of the gland to be given by

$$V = c(w_R w_L h_O - \pi r^2 h_O) \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (2)$$

where c is a constant, or, assuming a constant density for all thyroids, the mass M of the thyroid is related to its dimensions by an expression of the form

$$\frac{M}{h_O} = a w_R w_L - b \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (3)$$

where a and b are constants. This hypothesis could be tested by plotting M/h_O against $w_R w_L$ for a series of thyroids, when a linear relationship would show the assumptions to be true.

Equation (3), regarded as a purely empirical expression, suggests other similar ones for trial. If the heights of both lobes are measured, the average height, h_{av}, can be substituted for h_o, and the square of the width of the gland in the anterior projection, w_f^2, for $w_R w_L$. The possible combinations of these four variables give four dimensionally equivalent equations.

Results

The method was tested on 13 patients prior to thyroidectomy, as detailed in Table 2. The mass of each operation specimen was again corrected for the amount estimated by the surgeon not to have been removed. This was usually 1/8 of the whole, and if it was more, or other-

Table 2

Thyroid dimensions measured by the present method

Patient	Diagnosis	Corrected mass of surgical specimen (g)	Measured thyroid dimensions in cm					
			h_o	h_L	h_R	w_L	w_R	w_f
1	Primary thyrotoxicosis	25.7	5.9	5.4	5.75	4.25	3.75	5.1
2	Diffuse toxic goitre	107	8.4	8.4	7.95	6.6	6.9	8.7
3	Primary thyrotoxicosis	151	9.6	7.0	8.8	7.0	7.2	9.0
4	Primary thyrotoxicosis	38.8	5.8	5.8	3.8	5.95	4.9	6.25
5	Primary thyrotoxicosis	73.8	7.7	6.0	7.25	6.05	4.9	6.7
6	Primary thyrotoxicosis	40.9	6.0	6.0	6.85	4.85	4.52	5.85
7	Lymphadenoid goitre	56	5.3	4.95	4.55	5.2	5.6	—
8	Nodular colloid goitre	71.7	7.6	7.6	6.3	4.5	5.0	6.0
9	Toxic nodular goitre	120	7.6	6.9	5.7	5.3	5.2	8.3
10	Nodular goitre	150	8.3	8.3	5.8	7.8	8.7	—
11	Colloid goitre	157	6.4	6.4	4.6	6.9	7.2	—
12	Colloid goitre	57.1	9.2	9.0	7.5	6.8	6.3	—
13	Primary thyrotoxicosis	42	6.25	6.0	5.3	5.1	5.4	6.8

wise doubtful, as in one case where cysts were punctured during the operation, that case was not included in the series.

In analysing the results, the complete series was examined, and also the smaller series of diffuse toxic goitres comprising patients 1 to 6 and 13, all of whom were specifically diagnosed as having toxic, but not nodular goitres. The formulae proposed were fitted to the data by the method of least squares, giving for the full series the equations:

$$\frac{M}{h_{av}} = 0.502 w_R w_L - 4.837 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (4)$$

$$\frac{M}{h_O} = 0.415 w_R w_L - 3.371 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (5)$$

and for the smaller series:

$$\frac{M}{h_{av}} = 0.402 w_R w_L - 2.667 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (6)$$

$$\frac{M}{h_O} = 0.328 w_R w_L - 1.385 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (7)$$

$$\frac{M}{h_{av}} = 0.238 w_f^2 - 1.817 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (8)$$

$$\frac{M}{h_o} = 0.194 w_f^2 - 0.675 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (9)$$

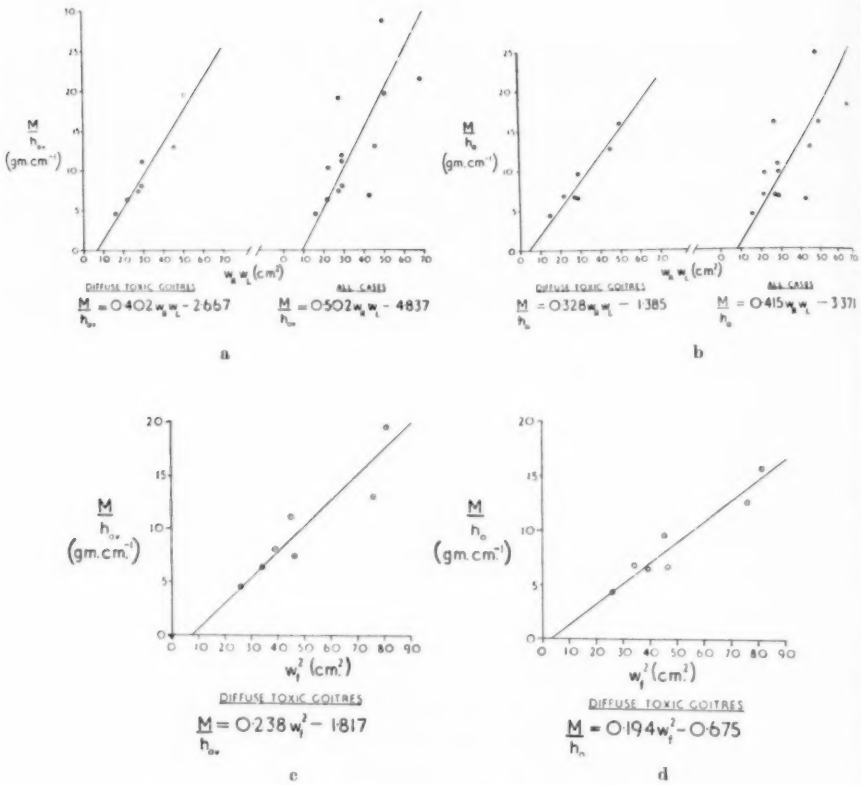
DIFFUSE TOXIC GOITRES
ALL CASES
M/h_w = 0·402 w_s w_L − 2·667
M/h_w = 0·502 w_s w_L − 4·837
a
M/h_o = 0·328 w_s w_L − 1·385
M/h_o = 0·415 w_s w_L − 3·371
b
M/h_w = 0·238 w_f² − 1·817
c
M/h_o = 0·194 w_f² − 0·675
d

Diagram 1. Fitting of equations (4) to (9) to the experimental data.

Each of these equations represents the bisector of the acute angle between the two lines of regression, since in each case, neither variable was known with complete accuracy. The anterior projected width of the thyroid, w_f, was regarded as being of secondary importance in these measurements, and was omitted if the patient's circumstances before the operation did not permit the full time to be spent on the measurements. It was measured in only two of the six miscellaneous cases, and so the full series has not been fitted to the equations involving w_f. The fitting of the above equations to the data is shown graphically in Diagram 1.

Using equations (4) to (9) to calculate the mass of each thyroid from its measured dimensions, the calculated values can be compared with the true masses to show the accuracy of the method, and the results of this

Table 3

Thyroid masses calculated from the measured dimensions

Patient	Corrected mass of surgical specimen (g)	Palpation estimate of thyroid mass (g)	Thyroid mass (g) from equations					
			(4)	(5)	(6)	(7)	(8)	(9)
[1]	25.7	30	17.7	19.1	21.0	22.7	24.5	25.8
[2]	107	120	148	130	128	114	133	118
[3]	151	100	162	168	139	145	138	144
[4]	38.8	40	47.1	50.7	43.5	47.5	35.8	40.0
[5]	73.8	60	66.3	68.8	61.0	64.2	58.7	62.0
[6]	40.9	20	39.6	34.4	39.4	34.9	40.5	35.8
7	56	120	46.4	46.1	—	—	—	—
8	71.7	50	44.9	45.3	—	—	—	—
9	120	50	56.8	61.4	—	—	—	—
10	150	80	206	206	—	—	—	—
11	157	90	111	110	—	—	—	—
12	57.1	90	138	132	—	—	—	—
[13]	42	70	50.8	50.4	47.5	47.8	51.9	51.8

[1] Denotes diffuse toxic goitre.

procedure are shown in Tables 3 and 4, along with the palpation estimates, again by a number of observers. The notation in Table 4 is the same as that in Table 1.

Discussion

The data on the seven diffuse goitres clearly fit the linear form of equation better than do those on the whole group, and the difference is probably significant. Calculating the standard errors of the standard deviations (Topping, p. 64) we find for equation (4)

$$\sigma = 0.497 \pm 0.102$$

and for equation (6)

$$\sigma = 0.156 \pm 0.045$$

The better fit is consistent with the observation that the diffuse goitres retained the general shape of the normal thyroid, whereas the other goitres frequently showed anomalies such as a greatly enlarged isthmus, or one lobe very much more enlarged than the other. Therefore only the diffuse goitres obey even approximately the assumption relating the mass to the dimensions.

Table 4

Accuracy of the present method

	Equation	$\bar{R}$	Maximum errors (%)	Average errors (%)	σ
All goitres (13 cases)	(4)	1.066	+ 141 — 52.7	+ 44.5 — 25.9	0.497
	(5)	1.056	+ 133 — 48.8	+ 42.4 — 25.9	0.469
	Palpation method	0.992	+ 114 — 58.3	+ 45.2 — 40.2	0.530
Diffuse toxic goitres (7 cases)	(6)	0.997	+ 20.3 — 18.5	+ 15.2 — 9.4	0.156
	(7)	1.000	+ 22.5 — 14.7	+ 14.4 — 10.8	0.146
	(8)	1.008	+ 24.9 — 20.5	+ 24.2 — 8.5	0.171
	(9)	1.006	+ 23.3 — 16.0	+ 9.3 — 11.0	0.135
	Palpation method	0.994	+ 66.7 — 51.1	+ 24.8 — 34.6	0.387

With the accuracy given by the equations derived from the data on the diffuse goitres, errors introduced by the correction for the thyroid remnant could be important, for the estimate of this correction is subjective. In the series of diffuse goitres it was 1/8 in each case, and so is not considered to invalidate the results.

Corresponding equations for the groups of 7 and 13 cases are not significantly different. Calculation of the errors in the coefficients is complicated by the fact that neither variable in the linear equations is known with much greater accuracy than the other, but, calculating the errors for equations (4) and (6), assuming first the values of M/h_{av} and then those of $w_R w_L$ to be accurate, it is found, choosing the smaller value of each standard error, that the equations may be written:

$$\frac{M}{h_{av}} = (0.502 \pm 0.116)\, w_R w_L - (4.837 \pm 3.513) \quad \ldots\ldots\ldots\ldots \quad (4a)$$

$$\frac{M}{h_{av}} = (0.402 \pm 0.059)\, w_R w_L - (2.667 \pm 1.958) \quad \ldots\ldots\ldots\ldots \quad (6a)$$

Therefore this sample is not large enough to reveal any real difference between the equations. A very much larger sample would also be needed to confirm the small differences in the accuracy with which the mass can be estimated using equations (6) to (9).

The palpation method is inferior to the counter method, though the diffuse goitres were estimated more accurately by palpation than the whole group, and the superiority of the counter method is most marked in the series of diffuse goitres.

In comparison with previous work, the best accuracy found here is about the same as that found by ALLEN and GOODWIN when testing the original empirical formula. It is somewhat better than that found by HIMANKA and LARSSON, and by KELLY, which in view of the success of the equations involving w_f, cannot be explained as a consequence of using more than one projected width. KELLY was careful to avoid nodular goitres in his series, and the improvement in this case is probably due to the increased accuracy of measurement with the slit collimator. In the case of HIMANKA and LARSSON, there is no record of the thyroids, which were necropsy specimens, being selected in any way, so that their sample may be more akin to the whole group in this work, their technique of outlining the specimen visually being more accurate than these counter measurements.

The slit collimator technique can be used with an I^{131} concentration in the thyroid of about 0.5 μC per g, so that the measurements can conveniently be performed 24 hours after a tracer dose of 50 to 100 μC with a thyrotoxic subject.

A difficulty peculiar to these tests was that many of the patients were undergoing preoperative iodine medication, making both uptake and half-life of the tracer dose unusually small. Therefore a dose of up to 1 mC had to be given and the measurements performed about 5 hours later.

The gland content was followed in three such cases, and the urinary excretion in two, with the results shown in Table 5. Patient D. M. L. was not included in the series because the correction to the mass of the operation specimen was considered too large and inaccurate, but for the dose calculation the thyroid mass was taken as 50 g, which is estimated not to be in error by more than about 20 %. The dose to the thyroid was calculated from the maximum uptake and biological half-life in the usual way, so that the figures give the dose to the thyroid remnant if the decay continued unchanged. The dose to the ovaries was estimated from the excretion of I^{131} in the urine. Urine was collected in three fractions at 8, 24 and 48 hours after the dose. The amount not recovered in the urine at the end of each interval was assumed to be all in the bladder, and the gamma ray dose to the ovaries calculated assuming them to be 4.5 cm from the centre of the bladder. This value is clearly a very rough estimate of the dose, but, since the ovaries receive most of their dose from the bladder, it should be an outside estimate, for much of the I^{131} in the body at any time is not in the bladder.

Table 5

Radiation dose to thyroid and ovaries in patients having preoperative iodine medication

Patient	I^{131} tracer (μc)	Maximum thyroid content (μC)	Biological half-life (days)	β-ray dose to thyroid (rep)	γ-ray dose to ovaries (r)
4, 1st series	810	147	0.39	6.8	—
9, 2nd series	316	45	0.5	3.0	—
13, 2nd series	435	—	—	—	1.2
D. M. L.....	440	20	1.18	7.0	0.9

The ovaries also receive beta-radiation from activity in the blood, and therefore this activity has been measured in two patients having iodine medication, using tracer doses of 40 μC. It was found that the dose to the blood was about 0.3 rep per mC administered, which is therefore the upper limit to the dose to the ovaries from this source. Thus it is concluded that the two tracers of about 440 μC gave doses to the ovaries of less than 1.5 equivalent roentgens, and hence that 1 mC, the largest dose given, would probably deliver less than 3.5 equivalent roentgens. The patient receiving the 1 mC dose was a married woman, aged 24, in the series testing the first method, but since this was a single exposure, amounting to less than 10 % of the recommended tolerance dose of 50 r to the gonads up to the age of 30 (Cf. "The hazards to man of nuclear and allied radiations"), it represents a negligible contribution to the genetic hazard. However, even such a dose level is unusual, and whenever possible, the measurements were performed before iodine medication, using a normal tracer dose.

Conclusions

The slit collimator technique enables the mass of a diffuse toxic goitre to be measured with reasonable accuracy. The restriction to this particular type of goitre is not severe from the point of view of dosimetry, since the condition is clinically well defined, and is the one most commonly treated with radioiodine.

For completely accurate dosimetry of I^{131}, the variation with time of the concentration of the isotope at every point in the thyroid would have to be known. In practice, the total activity in the gland is measured, so that the mass of the thyroid, as measured by the technique described here, leads to the value of the average dose to the gland. Since the follicles

which take up the isotope are presumably responsible for the patient's condition, the clinically significant dose is the average dose to those follicles which are active, *i. e.*, more nearly the maximum than the average dose. In this sense, the measured mass is an overestimate of the effective mass required for dosimetry, but it is impossible to allow for this without a detailed knowledge of the distribution of the activity. Fortunately, a diffuse goitre is the type most likely to show uniform uptake, though even here microscopic variations by a factor of 3 about the mean concentration have been reported (SINCLAIR et coll.).

The chief practical disadvantage of the method is the long time required to make the measurements. On the basis of the results presented here, however, the time can be shortened without loss of accuracy by measuring only the anterior projected width and the overall height of the thyroid, using equation (9) for the calculation. The measurement should then take 30 to 45 minutes.

Acknowledgements

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SUMMARY

To estimate the mass of the thyroid gland for the purposes of I^{131} dosimetry, a scintillation counter with a slit collimator is used, following a tracer dose of I^{131}, to measure the major dimensions of the gland. Four empirical formulae are proposed to relate the dimensions to the mass. In seven measurements of diffuse goitres, checked at operation, the method gave maximum errors of about + 23 % and — 17 %, with average errors of about + 16 % and — 10 %. The agreement was considerably poorer when six examples of other types of goitre were included.

ZUSAMMENFASSUNG

Zur Gewichtsbestimmung der Schilddrüse für die Dosimetrie des Radiojod wird nach Verabreichung einer Spurdosis von J^{131} ein Scintillationsrechner mit Schlitzkollimator benutzt, um die Grössenausdehnung der Drüse zu messen. Vier empirische Formeln werden vorgeschlagen, um die Dimensionen zum Gewicht in Beziehung zu setzen. Bei 7 Messungen diffuser Strumen ergab die Methode bei operativer Kontrolle einen maximalen Fehler von etwa + 23 % und — 17 % bei einem durchschnittlichen Fehler von + 16 % und — 10 %. Die Übereinstimmung war erheblich geringer, wenn man 6 Beispiele anderer Strumatypen miteinbezog.

RÉSUMÉ

Pour estimer le poids de la thyroïde en vue d'une dosimétrie de I^{131}, l'auteur a utilisé un compteur à scintillation muni d'un collimateur à fente, après administration d'une dose traceuse de I^{131}, pour mesurer les grandes dimensions de la glande. Il propose quatre formules empiriques reliant les dimensions au poids. Dans sept mesures de goîtres diffus, controlés opératoirement, cette méthode a donné des erreurs maximales d'environ + 23 % et — 17 %, avec des erreurs moyennes d'environ + 16 % et — 10 %. L'accord était beaucoup moins bon si on tenait compte de six exemples d'autres types de goîtres.

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THE COMBINED EFFECT OF HEAVY WATER AND ROENTGEN IRRADIATION ON THE ANIMAL ORGANISM

by

G. Häggqvist and *G. Hevesy*

The toxicity of concentrated heavy water was discovered shortly after it became available. REITZ and BONHOEFFER observed, for example, that *algae* when grown in water containing more than 80 % D_2O were considerably damaged. HÄGGQVIST et coll. (4, 5) recently replaced the drinking water of mice with pure or concentrated heavy water and investigated the effect of this replacement on various organs of the animals. The testicles were found to be especially sensitive to the effect of heavy water and the germinative epithelium was completely destroyed. While mitoses in intestinal mucosa cells were interfered with only to a minor degree, a marked concentration of chromosomes and a fragmentation of nuclei was observed. The cells of the reticulo-endothelial system of the liver, the lymph glands, and the spleen were enlarged. The sarcosomes of the heart muscles became readily visible. That the heart beats slower in heavy water is known from the work of BRANDT and REINDELL inter alios. Furthermore when a heart is first placed in heavy water and thereafter transferred to Ringer's solution it will beat for a longer time than a heart placed directly in the Ringer's solution.

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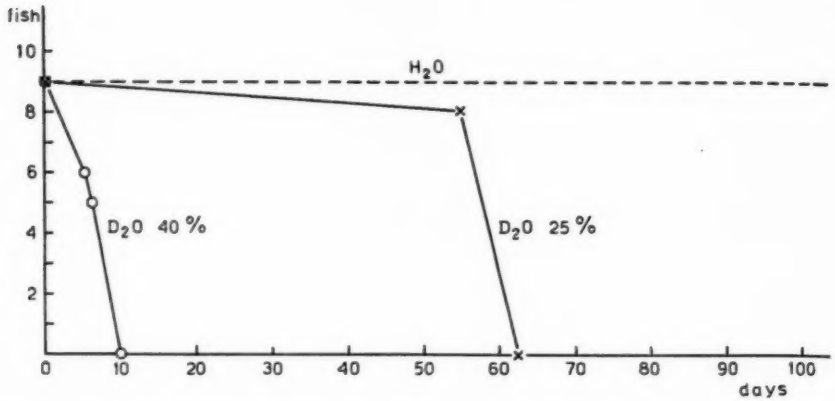

Diagram 1. Effect of heavy water on the life span of fish. The ordinate denotes the number of fish still alive.

Recently BUCHTHAL and ENGBAEK (2) found that the action potentials of the frog muscle placed in Ringer's solution containing heavy water differed markedly from the action potentials when ordinary Ringer's solution was employed. SVENSMARK observed that the mechanical response of the muscle was influenced even when the Ringer's solution contained not more than 25 % D_2O.

Heavy water was also found by HÄGGQVIST et coll. (4) to be radiomimetic and it seemed to be of interest to combine the administration of heavy water and roentgen irradiation and study their combined effect. The mice which had drunk D_2O had in our experiments a lower mortality following exposure to 700 r than those which had drunk H_2O. These results could, however, not be reproduced later; the difficulty of this type of experiment is mainly due to the varying willingness of mice to drink heavy water. This induced us to replace the mice in such experiments by fish, since fish are known to obtain an exchange equilibrium with the surrounding water within a short time. Most of the water in goldfish kept in diluted heavy water was found to attain exchange equilibrium in the course of an hour (3).

Experiments with fish

Hyphessobrycon Scholzei weighing 150 to 380 mg were placed in (150 to 300 ml) 10 to 40 % heavy water to which the solid components of a corresponding volume of tap water were added. The controls were

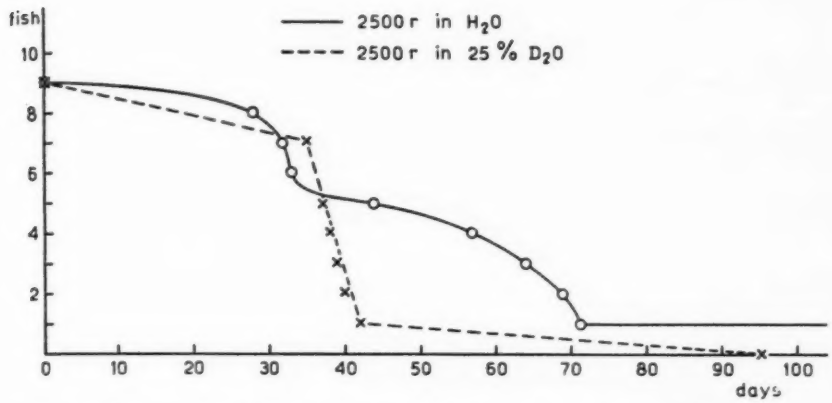

Diagram 2. Fish exposed to 2,500 r in tap water and in water containing 25 % D_2O. The ordinate denotes the number of fish still alive.

kept in tap water. The heavy water was purified at intervals by distillation. When placed in 50 % D_2O solution the fish were obviously much disturbed, but when kept for a while in water of a lower D_2O content which was stepwise increased, the fish showed less but still marked signs of distress. In 40 % D_2O the behaviour of the fish was normal but their life span was considerably shortened as may be seen from Diagram 1. While the controls lived for hundreds of days, fish kept in 40 % heavy water died within 10 days, and in 25 % heavy water within 62 days.

In all our experiments, which were carried out at 20° C, fish were kept for 3 days in 10 to 40 % heavy water. They were then exposed to 2,500 to 3,000 r (165 kV, 1 mm Al, 425 r/min) in heavy water through which oxygen bubbled and were placed after irradiation in tap water. The fish were exposed in small Petri dishes made of thin-walled plastic material, the height of the water column being 1 cm. While half of the fish exposed in tap water to 2,500 r died within 51 days, they survived only for 37 days when similarly exposed in 25 % D_2O. When exposed to 3,000 r the corresponding figures were 22 days and 15 days. Keeping fish for 3 days in 25 % heavy water without exposing them to roentgen rays did not shorten their life span.

When fish are exposed to irradiation in heavy water, damaging radicals which in part contain deuterium instead of protium are produced and these may be more noxious than the radicals free from deuterium. Some of the body constituents of the fish also contain deuterium and their metabolic pattern differs correspondingly from that of the body constituents free from additional deuterium. All these factors may be

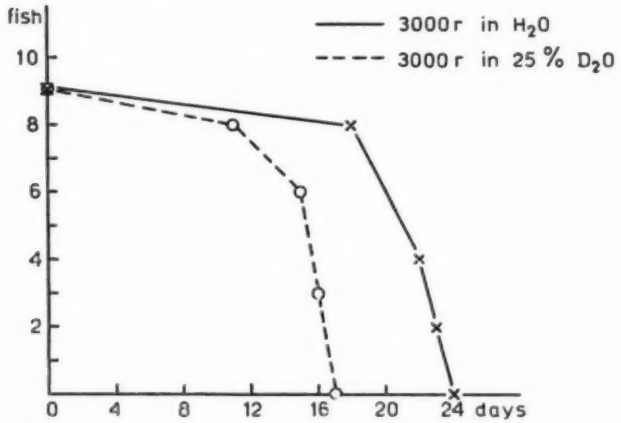

Diagram 3. Fish exposed to 3,000 r in tap water and in water containing 25 % D_2O. The ordinate denotes the number of fish still alive.

responsible for the greater mortality of fish exposed to irradiation in heavy water.

One may attempt to divide the 'radical effect' from the 'biochemical effect' by varying the time under which the fish are kept in heavy water prior to irradiation and also by varying the temperature of the latter, as replacement of hydrogen by deuterium is accelerated by increased temperature (8). Some minutes only after moving a frog muscle from normal Ringer's solution to one containing 25 % D_2O its contractions, however, are already found to be markedly reduced (7). In view of this and similar observations a division of the radical effect from the biochemical and physiologic effects is quite a difficult task.

Acknowledgments

The support of this investigation by the Alice and Knut Wallenbergs Stiftelse and the assistance of Mrs. Ulla Österman is gratefully acknowledged. The thanks of the authors are also due to Dr. Arne Forssberg for irradiating the fish.

SUMMARY

Fish (*Hyphessobrycon Scholzei*) irradiated in 25 % heavy water with 2,500 and 3,000 r and kept after irradiation in tap water are more damaged than when exposed to irradiation in tap water. The half-life time of fish after exposure to 2,500 r in tap water amounts to 51 days, in 25 % heavy water to 37 days. The corresponding figures after 3,000 r are 22 and 15.

ZUSAMMENFASSUNG

Fische (*hyphessobrycon Scholzei*), welche man in einer 25 %-Lösung von schwerem Wasser mit 2,500 und 3,000 r bestrahlt und danach in Leitungswasser aufbewahrt, werden mehr geschädigt als wenn sie in Leitungswasser bestrahlt werden. Die mittlere Überlebenszeit der Fische nach Exponierung mit 2,500 r in Leitungswasser beträgt 51 Tage, und bei Exponierung in 25 %-igem schweren Wasser 37 Tage. Die entsprechenden Prozentzahlen nach 3,000 r sind 22 und 15.

RÉSUMÉ

Des poissons (*hyphessobrycon Scholzei*) irradiés dans de l'eau lourde à 25 % par 2,500 et 3,000 r et mis après irradiation dans de l'eau du robinet sont plus lésés que ceux qui ont été exposés à l'irradiation dans de l'eau du robinet. Le temps de demi-vie des poissons après irradiation par 2,500 r dans l'eau du robinet est de 51 jours, dans l'eau lourde à 25 % de 37 jours. Les durées correspondantes après 3,000 r sont de 22 et 15 jours.

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BOOK REVIEWS

EFFECT OF RADIATION ON HUMAN HEREDITY. Report of a study group convened by WHO together with papers presented by various members of the group. 168 pp. WHO, Geneva 1957. $ 4.00.

In August 1956 a study group convened by the World Health Organization discussed the effect of radiation on human heredity at the University of Copenhagen under the chairmanship of Alexander Hollaender. The group consisted of twenty specialists from the United Kingdom, the United States, Denmark, Canada, Brazil, Germany, India, France and Sweden and represented various branches of animal and human genetics, radiophysics, radiobiology, radiotherapy and statistics. The first part of the published report contains the views of the group as a whole, particular emphasis being placed on the lines of research that should be followed in the future. The second part consists of twelve papers contributed by various individual members of the group. The group has been able to reach agreement on several important points. It is stressed that all man-made radiation must be regarded as harmful to man from the genetic point of view. From available quantitative knowledge regarding the basic mechanisms of genetics, there are strong grounds for believing that most genetic effects are very closely additive so that a small amount of radiation received by each of a large number of individuals can do an appreciable amount of damage to the population as a whole. There are many gaps in the knowledge, however, concerning these effects in man. These gaps will be closed only after a great expansion of general and ad hoc research in genetics and other fields of biology. The importance of recording radiation exposure in individuals and populations is stressed. To avoid the accumulation of excessive exposure through lack of information, the doses received by individuals should be recorded systematically. It could be expected that such recording would cut down the exposures given in medical diagnosis and treatment, since it would impress radiologists and technicians of the magnitude of such exposures. Furthermore, it would be necessary to collect information on the exposure to the gonads, received at each age in individuals and on an average per head of population. It should be possible to recognize the amount of exposure received by the parents of a given child, information particularly valuable for the purposes of genetic analysis.

With regard to future research, the committee is of the opinion not only that as much experimental work as possible should be done on radiation effects on suitable organisms and such controlled observation studies as offer in man, but that there should be an intensification of all human and experimental genetic research. Specifically, the group urges research in a number of particular fields where gaps in knowledge are most apparent and where information is urgently needed. The following main lines are mentioned: further study of spontaneous and artificially induced mutation; mutational component in the somatic changes produced by radiation and other means; means of protection

against mutagenic agents; development of new and improved techniques for the identification of mutants; manner of gene action; selective factors in populations with particular reference to the special conditions in man; patterns of mating in human populations and their genetic implications; twin studies in man involving standardized registration of twins in various countries; determination of the frequency of diseases with a significant genetic component, with particular reference to their epidemiology; study of isolated populations of special genetic interest; genetic mapping of human chromosomes; human cytology and cytochemistry; and development of further statistical methods. The committee recommends furthermore the establishment of more institutions devoted to general genetics and human genetics. They consider it essential that instruction in genetics should be given to all scientists, particularly those whose work is likely to involve the use of radiation and radioactive materials in research. Other recommendations concern the registration of serious hereditary diseases and defects in various populations, international cooperation in training and research, effect of radiation on the life-span, and the necessity of shielding the gonads from radiation exposure.

The second part of the book contains papers by H. J. Muller (damage from point mutations), T. C. Carter (mutations at known gene loci in irradiated animal populations), B. Wallace (problems connected with an increase of mutation rates in Mendelian populations), R. M. Sievert (exposure of man to ionizing radiations), J. Lejeune (induced mutations in offspring of irradiated parents), W. M. C. Brown (gonad doses from medical radiology), L. S. Penrose (mutation in man), A. R. Gopal-Ayengar (areas with different background-radiation levels), A. C. Stevenson (comparison of mutation rates at single loci in man), J. V. Neel (estimation of mutation rates in animals and man), N. Freire-Maia (effect of inbreeding on hereditary traits), and H. B. Newcombe (detection of genetic trends in public health). Representing the opinions of the individual workers, these papers contain much valuable information and will be helpful to anybody interested in radiation and heredity. The volume would have gained much in value, however, if at least the general trend of the discussions following the individual papers or preceding the final conclusions of the group could have been included.

Georg Klein.

L'ARTHROGRAPHIE OPAQUE DU GENOU. Par Paul Ficat. 243 pages, 139 figures. Masson et Cie, Paris 1957. 3,800 fr.

Arthrography has widened the field of knowledge on internal derangement of the knee. Opinions vary concerning the best contrast medium in this investigation; the author of this book is a warm supporter of opaque contrast media, and regrets that they are so little used in France.

The author, who is both a radiologist and a surgeon, describes his experiences with a series of more than 600 cases of arthrography of the knee, all examined by LINDBLOM's technique. All examinations and surgical procedures were performed by the author himself.

The normal, malformed, and injured menisci as they appear in roentgen films are described clearly. The high proportion of correct diagnoses illustrates the reliability of arthrography, and accords with Lindblom's findings. The description of the joint cartilage opens interesting views on the problem of arthrosis. The author considers arthrography to be of secondary importance in diagnosing injuries of the ligaments. The experience of the reviewer is that the diagnosis of injuries of the cruciate ligaments is greatly facilitated by tomography in combination with arthrography.

The illustrations are good and they are accompanied by explanatory diagrams. This well-written book is warmly recommended to all those interested in the field.

Stig Fagerberg.

SYSTEMIC RETICULOENDOTHELIAL GRANULOMA. By Per Westling, Kurt Sundberg, and Gunnar Söderberg. 66 pages, 32 illustrations. Acta radiol. Suppl. 149 (1957). Sw. Kr. 25:—.

Evidence has been accumulating since about 1940 that Hand-Schüller-Christian's disease, Letterer-Siwe's disease, and eosinophilic granuloma of bone, are variants of a single morbid systemic condition associated histologically with granulomatous lesions. The cytologic picture is dominated by reticuloendothelial cells. We therefore subscribe to the denomination of systemic reticuloendothelial granuloma proposed in 1940 by the Swedish pediatrician WALLGREN. Sixteen cases of this disease, treated at Radiumhemmet, Stockholm, have been studied by the authors who make up a team consisting of a radiotherapist, a radiologist and a pathologist.

Following a review of the literature with special reference to works which have advanced the concept of a single disease entity, a summary is given of the principal histologic and patho-physiologic data as well as a description of the more important signs. The roentgen examination is very important. Skeletal lesions are present in virtually every case, and have certain characteristic features. The commonest situation is the calvaria, followed by the pelvis; the acetabular regions appear to be the zones of predilection. The lesions originate in the bone marrow, are of an osteolytic character, and are usually discrete. They produce no endosteal reaction, but if perforation of the cortex occurs, periosteal reaction may appear. It is pointed out that skeletal lesions sometimes produce no symptoms; this indicates roentgen examinations of the whole skeleton, which may have to be repeated.

Roentgen treatment of the skeletal lesions produce a good local effect and surgery seems to have no place other than for biopsy purposes. The roentgen treatment soon ameliorates the local pain and leads to new bone formation. Not infrequently the lesions tend to heal spontaneously although this is unpredictable. On comparing treated and untreated lesions in the same patient, good regression of the former but progression or no change of the latter was noted. The roentgen doses need not be high; a tissue dose of 400 to 800 r is probably sufficient in most cases. The diagnostic problems are discussed. It is noteworthy that many cases are mis-diagnosed as malignant tumours. The importance of satisfactory cooperation between clinicians, radiologists, and pathologists in the diagnostic procedures is emphasized.

Autoreview.